Sleep-disordered breathing (SDB), which includes obstructive sleep apnea (OSA) as its most extreme variant, is characterized by intermittent episodes of partial or complete obstruction of the upper airway during sleep that disrupts normal ventilation and sleep architecture and is typically associated with snoring and daytime sleepiness. SDB is common, with an incidence in middle-aged men and women of 4% and 2%, respectively.1 Major risk factors for SDB include obesity, male gender, increasing age, and abnormalities of craniofacial morphology.2

There is an increasing perception that SDB/OSA via various mechanisms increases cardiovascular morbidity and mortality (Figure 1). However, many risk factors for SDB/OSA, such as obesity and male gender, are the same as for hypertension and cardiovascular disease.3 Thus, only recently has there been converging evidence that SDB is a risk factor for their development.4–6 Moreover, there is increasing information to indicate that SDB/OSA is linked to metabolic, vascular, hematologic, and genetic markers associated with increased cardiovascular disease risk. In addition, central sleep apnea (CSA), another form of SDB, appears to be an important factor that influences morbidity and mortality among those with heart failure (HF). Nevertheless, responsible mechanisms, the role of SDB as a risk factor “independent” of associated comorbidities, and whether treatment of SDB will mitigate this risk are unknown and remain to be determined.

This report summarizes the proceedings of a workshop sponsored by the National Center on Sleep Disorders Research and the National Heart, Lung, and Blood Institute on September 12 to 13, 2002, to assess a broad array of new physiological, molecular, and genetic information pertaining to the relationship between SDB and cardiovascular diseases. The major goal of the workshop was to recommend new directions for the research required to better understand the pathophysiological mechanisms underlying the relationship between SDB and cardiovascular diseases and the extent of this association from an epidemiological perspective.

Hypertension, Vascular Disease, and Sleep-Disordered Breathing

Epidemiology
Consistent data indicate that individuals with SDB/OSA have a higher prevalence of hypertension.4,5 Findings from the Wisconsin Sleep Cohort Study demonstrate a 3-fold increased risk of incident hypertension over a period of 4 years independent of other known risk factors.6 Equally important are observations that experimentally induced OSA in a canines results in daytime hypertension.7 Hypertensive patients whose blood pressures do not fall appropriately at night, or “non-dippers,” are at increased risk for cardiovascular damage. Patients with SDB frequently have repetitive episodes of blood pressure elevation in conjunction with their apneic episodes,8 and they may be particularly likely to manifest a non-dipper pattern.9 Moreover, some individuals with SDB have hypertension that is not controlled despite the use of multiple antihypertensives.10 Recent data suggest that treating OSA lowers not only nighttime but also daytime blood pressure.11

Pathophysiological Mechanisms Linking SDB to Hypertension
Experimental and clinical studies demonstrate that sympathetic overactivity, an important mechanism in the pathogenesis of hypertension, occurs with SDB. Repetitive episodes of airway occlusion with hypoxia, hypercapnia, and the dramatic changes in intrathoracic pressures result in diverse autonomic, humoral, neurohumoral, and hemodynamic responses. These may affect cardiovascular function during the day even when breathing is normal.8 Urinary catecholamines are elevated in untreated OSA subjects and return to control levels after effective treatment of apnea.12 In both children and adults, sympathetic overactivity is associated with SDB.8 Sympathetic stimulation can contribute to insulin resistance and can modulate leptin expression, facilitating the development of a vicious cycle of worsening obesity, hypertension, and SDB. A major physiological result of repetitive nocturnal

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SDB events is intermittent, often profound hypoxemia. Intermittent hypoxemia is known to activate the sympathetic nervous system both acutely and chronically.

Increasing evidence links SDB-related hypertension to endothelial dysfunction. Endothelial cells produce a number of vasoactive and physiologically important substances, including endothelin (ET-1), which induces vasoconstriction, and nitric oxide (NO), which results in vasorelaxation. In patients with SDB, nocturnal hypoxemia results in a significant elevation in plasma ET-1 and an increase in blood pressure. The hypertensive effects of ET-1 may lead to sustained daytime blood pressure elevations. Effective treatment of SDB by continuous positive airway pressure (CPAP) lowers ET-1 levels and blood pressure.13 Endothelial cell production of NO seems to be diminished in patients with SDB contributing to impaired vasodilation and a higher resting vascular tone. Inflammation may be an important contributor to endothelial dysfunction in SDB as well. Hypoxemia and sleep deprivation each induce production of proinflammatory cytokines.14 Indeed, patients with SDB have higher levels of C-reactive protein compared with closely matched control subjects.15 Activation of inflammatory mechanisms may have direct effects on impairing endothelial function in patients with SDB, resulting in impaired vasodilation and a higher blood pressure.

Hypercoagulability, Thrombosis, and Sleep-Disordered Breathing

Epidemiology
Patients with pulmonary embolism or deep vein thrombosis have a higher incidence of SDB.16 Platelet aggregation as well levels of plasminogen activator inhibitor-1 and fibrinogen are increased in SDB patients and decrease after CPAP treatment.17,18 In addition, hypertensive SDB patients have been noted to have higher levels of thrombin-antithrombin complexes and D-dimer.19 However, it is unclear whether these increased levels are related to hypertension associated atherosclerotic vascular disease or whether they contribute independently to SDB. Available studies are limited by small sample size, lack of uniform definition of SDB, and failure to consistently control for potential confounders such as body mass index or smoking.

Pathophysiological Mechanisms Linking SDB to Hypercoagulability
Several potential mechanisms could explain the association between SDB and a hypercoagulable state. First, superoxide release from neutrophils in SDB patients may be excessive.20 This might limit bioavailable NO and enhance thrombus formation. Second, levels of catecholamines are increased in SDB patients, resulting in activation of platelet adrenergic receptors and enhanced aggregability. Third, hypertension itself appears to result in a hypercoagulable state. Finally, there seems to be a genetic predisposition toward both increased thrombosis and SDB.21

Sleep-Disordered Breathing and Coronary Artery Disease

Epidemiology
The last half of the 20th century has seen a peaking of coronary heart disease (CHD) mortality followed by a gradual fall in the age-adjusted rates. Greater survival of individuals has resulted in an increased prevalence of chronic CHD and a higher mortality from complications such as HF. In an older population with increased prevalence of CHD and multiple co-morbidities, SDB may assume the role of an independent risk factor.

Case control and retrospective studies have indicated that SDB is associated with an increased prevalence of CHD and CHD related outcomes.22,23 Only recently have large-scale cohort studies confirmed these findings. In the Sleep Heart Health Study (SHHS), several cardiovascular disease outcomes, including myocardial infarction and stroke, were found to be associated with SDB.24 The Nurses Health Study prospectively observed that self-reported snoring, a cardinal symptom of SDB, may be an independent risk factor for the development of CHD.6

Cardiovascular Disease Risk Factors
Defining the precise risk of CHD attributable to SDB is difficult because those with the latter have been recognized to have comorbidities such as obesity, hypertension (vide supra), and hyperlipidemia that place many at higher risk for cardiovascular disease (CVD). Nevertheless, the SHHS showed that there was a stepwise increase in CVD risk factor levels with greater severity of SDB.3 These factors included age, male gender, obesity, diabetes, hypertension, and lipid levels. Lipid abnormalities in those with SDB appeared related to obesity, a major risk factor for SDB severity. SDB also appears to be associated with insulin resistance.25 Thus, defining the interactions between SDB, weight, and body fat distribution are essential to further understanding how CVD risk factors relate to SDB.

Recently, evidence has accumulated to show that patients with uncomplicated hypertension often have insulin resistance as part of the “metabolic syndrome.” Insulin, besides its metabolic effects, exerts significant actions on the sympathetic nervous system and NO release. These activities can be involved in the short-term and long-term control of vascular
tone and circulating volume and may affect blood pressure. Sleep deprivation contributes to the development of insulin resistance as well as other metabolic and endocrine alterations, such as abnormalities in cortisol, growth hormone, and leptin secretion. These observations strongly suggest sleep loss, including that attributable to SDB, has an adverse impact on components of the metabolic syndrome and may represent a risk factor for obesity.

As previously emphasized, obesity is a major risk factor for SDB, hypertension, and cardiovascular disease. Body fat content is usually tightly controlled by a homeostatic mechanism linking adipocyte mass with central nervous system control of appetite and metabolic rate. The adipocyte-derived hormone leptin acts as the afferent signaling limb of this negative feedback loop to decrease appetite and increase energy expenditure. Paradoxically, human obesity is associated with hyperleptinemia, suggesting resistance to leptin’s actions. Patients with OSA may be at increased risk for weight gain. Resistance to appetite-suppressant effects of leptin might be involved because OSA patients have higher leptin levels than similarly obese controls. Furthermore, increased leptin levels associated with SDB decline after treatment with CPAP.

The generation of reactive oxygen species (ROS) is one mechanism by which obesity and SDB might interact to adversely affect cardiovascular morbidity and mortality. An increase in ROS can upregulate vascular adhesion molecules, cause platelet aggregation, and scavenge the potent vasodilator NO. Obesity is associated with increased ROS levels. SDB represents a likely mechanism linking obesity and elevated ROS. Increased ROS levels are found in SDB, and treatment of SDB with nasal CPAP decreases those levels.

Another mechanism could be the secretion of adipokines such as leptin, adiponectin, tumor necrosis factor-α, and interleukin 6. Many of these adipokines have known roles in the development of hypertension and atherosclerosis. Moreover, differential expression of these adipokines between subcutaneous and visceral fat may account for specific cardiovascular risks between those with (greater visceral obesity) and without SDB.

Pathophysiology of Coronary Heart Disease and Its Relationship to SDB
Increasing evidence indicates that inflammation is important in the pathogenesis of acute coronary disorders, related in large part to initiation or perpetuation of endothelial injury. Several mechanisms are proposed for inducing atherosclerotic endothelial injury. These include latent, subclinical infection from viruses and/or chlamydia, increased oxidative stress, genetic susceptibility, and direct endothelial injury. On a cellular level, plaque rupture and endothelial injury are produced by entrance of activated monocytes/macrophage into plaques, release of inflammatory mediators from platelets, and loss of local defense mechanisms against thrombosis.

Several causal pathways potentially connect SDB to acute and chronic coronary heart disease, but there is a paucity of definitive evidence. One well-studied pathway involves chronic hypertension, but it is often forgotten that SDB is associated with repeated blood pressure surges during the night and substantial cumulative exposure to high blood pressure even in the absence of daytime hypertension. Likewise, SDB seems to be associated with left ventricular hypertrophy, a known predictor of CVD events, even in the absence of daytime hypertension. Recent intriguing work suggests that hypoxia, a frequent consequence of SDB, might trigger a generalized inflammatory response, causing systemic release of inflammatory mediators such as C-reactive protein, fibrinogen, interleukin 6, and adhesion molecules, all of which have been implicated in CHD.

Sleep-Disordered Breathing and Heart Failure
Epidemiology of SDB in Heart Failure
The prevalence of HF is increasing in the United States. HF is now viewed as a spectrum of cardiac dysfunction with asymptomatic cardiovascular disease on one end extending to left ventricular failure on the other. Asymptomatic systolic dysfunction (<40% ejection fraction) occurs in ~2% of the general population. Furthermore, it is increasingly recognized that diastolic dysfunction is common and is a major risk factor for the development of overt congestive heart failure (CHF) and subsequent cardiac mortality.

OSA is common in patients with HF. In addition, CSA, a nonobstructive form of SDB, is frequently observed in those with HF. One third of those with HF and SDB have CSA. The main risk factors for OSA in patients with HF are obesity in men and age greater than 60 years in women. Risk factors for CSA in HF are male sex, hypocapnia, atrial fibrillation, and age greater than 60 years. CSA is also highly prevalent in patients with left ventricular dysfunction even before the development of overt HF. The main clinical significance of CSA in HF is its association with increased mortality independent of other known risk factors. The presence of OSA in patients with overt HF has the potential to worsen ventricular dysfunction. However, the role of SDB in patients with asymptomatic left ventricular dysfunction is not known.

Pathophysiology of Heart Failure and SDB
HF is the common final pathway of several possible pathogenetic mechanisms. Hypertension and ischemia are responsible for the majority of cases in the developed world. Irrespective of the initiating factor, injury to myocytes and cardiac extracellular matrix leads to ventricular remodeling, neurohumoral activation, increased inflammatory cytokine production, oxidative stress, apoptosis, and altered gene expression. Further myocardial cell injury and ventricular remodeling result, with eventual clinical CHF.

The presence of SDB can potentially worsen or initiate this downward pathological spiral, as suggested by data from a canine model. In the short-term, inspiration against an occluded upper airway generates exaggerated negative intrathoracic pressure, leading to both an increase in left ventricular afterload, and a decrease in left ventricular preload. The net effect is a reduction in stroke volume. Intermittent hypoxia may impair cardiac contractility and induce an oxygen supply-demand mismatch provoking myocardial ischemia in those with pre-existing coronary artery disease. Sympathetic vasoconstrictor outflow produces inter-
mittent hypertension, further increasing afterload. These effects are more pronounced in subjects with than in those without HF. Valida
tion for a causal relationship between OSA and HF is supported by information obtained from treatment paradigms. Use of CPAP in dilated HF decreases left ventricular end systolic volume and improves ejection fraction. In contrast to OSA, CSA is most likely to be the consequence of HF rather than its cause. CSA is caused by oscillations in PaCO2 above and below the threshold for apnea. HF patients with CSA are generally hypocapnic because of the combined effects of pulmonary congestion, causing stimulation of vagal irritant receptors, increased central and peripheral chemosensitivity, and arousals from sleep. The pathophysiological effects of CSA on the failing heart are similar to those caused by OSA, except that negative intrathoracic pressure is not generated during apneas.

Although CSA is not generally the cause of HF, treatment of CSA can have beneficial effects. Use of CPAP in HF patients with CSA improves left ventricular ejection fraction and mortality. Sleep Disordered Breathing and Cardiac Arrhythmias

Epidemiology There are many different types of arrhythmias that have been linked to SDB. Atrial and ventricular premature extrasystoles are common. Other tachyarrhythmias, such as persistent supraventricular tachycardia, atrial fibrillation, or flutter, and ventricular arrhythmias, in particular sustained or nonsustained ventricular tachycardia, are more likely to occur in the setting of preexisting structural heart disease. However, there is a wide discrepancy in the reported prevalence of all types of cardiac arrhythmias. Moreover, conclusions as to whether arrhythmias are more common among those with SDB are conflicting. In some studies, it appears that arrhythmias were more common in SDB patients who had severe nocturnal hypoxemia during REM sleep. A recent study among patients who had undergone successful cardioversion for atrial fibrillation demonstrated an 82% rate of recurrence over a 12-month period in contrast to a 42% and 53% rate of recurrence among OSA patients treated with CPAP and controls who did not undergo a sleep study, respectively.

Unresolved is the role of SDB as an independent risk factor for cardiac arrhythmias, and in particular, for life-threatening arrhythmias. Successful treatment for SDB seems to decrease arrhythmias. However, no study has addressed the independent role of SDB on arrhythmic death as opposed to the confounding effect of coexisting diabetes and cardiovascular disease. For the relationship between SDB and arrhythmias to be clarified, carefully designed prospective studies are necessary.

Pathophysiology There are several possible mechanisms by which arrhythmias would occur more commonly or be more severe in the presence of SDB. During obstructive events, there is an increase in myocardial wall tension and hence in O2 demand. This could result in myocardial ischemia. In addition, hypoxemia and hypercarbia occurring as a result of SDB could lead to cortical arousals, increased sympathetic tone, and catecholamine release. Such mechanisms have the potential for being responsible for excess mortality from SDB in the setting of heart disease, but this needs to be determined.

Sleep-Disordered Breathing and Cardiovascular Disease: Role of Gene–Environmental Interactions Candidate genes for OSA include those that influence obesity and body fat distribution, craniofacial morphology, ventilatory control, and the sleep-wake state. Such genes may be expected to influence a number of phenotypes related to OSA. For example, although leptin regulates body weight and levels are increased in obesity, it may also influence lung growth and respiratory control and influence sleep architecture. ET-1 not only is a potent vasoactive peptide that potentially influences blood pressure, but also can affect control of ventilation.

The prevalence of diabetes, central obesity, hypertension, hyperlipidemia, and insulin resistance have each been reported to be high in OSA, affecting 30% to 90% of OSA cases. The association of OSA with insulin resistance could be based on genetic defects leading to visceral obesity and/or diabetes with several secondary effects (e.g., hypertension, cardiovascular disease and OSA). Alternatively, OSA and cardiovascular disease/hypertension may be linked in a more direct causal pathway because of OSA-associated sympathetic nervous system activation or hypoxemia, which exacerbates insulin resistance. Several environmental factors, such as the use of sedative medications and alcohol, may exacerbate SDB/OSA severity; these factors may be of greatest relevance in individuals with a genetically determined susceptibility to upper airway collapse. Social or biological causes of insufficient or fragmented sleep may also exacerbate SDB/OSA by altering ventilatory control, or, as previously discussed, by producing neurohumoral abnormalities. Poor diet and lack of physical activity are key determinants of obesity, and could thus also exacerbate SDB/OSA. Chronic infections may promote lymphoid hyperplasia, causing adenoidal and tonsillar hypertrophy, important risk factors for OSA in children.

Potential Role of SDB Treatment in Reducing Cardiovascular Disease Risk Randomized clinical trials eventually will be required to determine whether treatment of SDB will be effective in reducing the risk of developing or dying of cardiovascular disease. Such studies will likely be large if they parallel the design of other cardiovascular disease intervention trials to control for confounders and any ethnic disparities. Before undertaking such trials, there is an urgent need to develop simpler screening tools to identify individuals with SDB (Figure 2). Moreover, there will be a need to gain a better understanding of the underlying pathophysiological mechanisms and the magnitude of the potential benefit from therapy of SDB. Although such trials could be designed initially using
In those with SDB, is there an inherited predisposition to a morbid event? A number of mechanisms could potentially explain the relationship between hypercoagulability/thrombosis and SDB, definitive data from larger well-controlled studies is lacking. Additional studies, which might be best performed in animal models, will need to consider that differential effects may be present because all blood vessels are not alike. Receptors for inflammatory mediators may be dissimilar according to the type and/or size of blood vessel.

The relationships among inflammatory biomarkers, vascular disease/endothelial dysfunction, hypertension, and SDB have been inadequately explored.

### Hypertension, Vascular Disease, and SDB
- The pathophysiological link between sympathetic dysfunction and target organ change and structural damage in blood vessels is not well understood. Additional studies, which might be best performed in animal models, will need to consider that differential effects may be present because all blood vessels are not alike. Receptors for inflammatory mediators may be dissimilar according to the type and/or size of blood vessel.
- The relationships among inflammatory biomarkers, vascular disease/endothelial dysfunction, hypertension, and SDB have been inadequately explored.

### Hypercoagulability, Thrombosis, and SDB
- Although small clinical series and case-control studies suggest a linkage between hypercoagulability/thrombosis and SDB, definitive data from larger well-controlled studies is lacking.
- A number of mechanisms could potentially explain the relationship between hypercoagulability/thrombosis and SDB, but relevant ones have not been defined.
- In those with SDB, is there an inherited predisposition to a hypercoagulable state such that only some patients are at risk?

### Deficits in Current Knowledge and Research Recommendations
The relationship between SDB and cardiovascular disease is complex, but improved understanding has profound implications for the care of the large number of individuals with both conditions. Although recent developments have advanced our knowledge concerning this relationship, there are a number of areas that require additional investigation. The following are the consensus of workshop participants of those areas in which there are substantial gaps in our knowledge and thus represent opportunities for future research.

### Hypertension, Vascular Disease, and SDB
- The pathophysiological link between sympathetic dysfunction and target organ change and structural damage in blood vessels is not well understood. Additional studies, which might be best performed in animal models, will need to consider that differential effects may be present because all blood vessels are not alike. Receptors for inflammatory mediators may be dissimilar according to the type and/or size of blood vessel.
- The relationships among inflammatory biomarkers, vascular disease/endothelial dysfunction, hypertension, and SDB have been inadequately explored.

### Hypercoagulability, Thrombosis, and SDB
- Although small clinical series and case-control studies suggest a linkage between hypercoagulability/thrombosis and SDB, definitive data from larger well-controlled studies is lacking.
- A number of mechanisms could potentially explain the relationship between hypercoagulability/thrombosis and SDB, but relevant ones have not been defined.
- In those with SDB, is there an inherited predisposition to a hypercoagulable state such that only some patients are at risk?

### Consequences of Sleep-Disordered Breathing
- Is there a role for antithrombotic therapy in some individuals with SDB irrespective of any effect of such therapy on comorbid conditions?

### Sleep-Disordered Breathing and Coronary Heart Disease
- There is a need to determine the mechanisms underlying the increased risk of cardiovascular disease conferred by SDB. If SDB is an independent risk factor for cardiovascular disease, is its effect mediated directly by alterations in autonomic nervous system function, increases in oxidative stress or enhancement of inflammatory processes? Alternatively, is the association between SDB and increased CHD risk mediated primarily through the acceleration of obesity, insulin resistance, and hypertension?
- Are there particular SDB subpopulations at higher risk for CHD, and are there genetic markers that might identify these individuals?
- The interactions among obesity, sleep deprivation and fragmentation, insulin resistance, and hypertension as they relate to SDB and CHD remain complex and not entirely well understood. Mechanisms responsible for these complex relationships should be identified.
- The role of SDB-induced alterations in leptin and other inflammatory mediators and the effect of these changes in the initiation or propagation of endothelial injury need to be better defined.
- The prevalence of SDB in those with asymptomatic heart disease has not been precisely defined.
- Among those with SDB, the prevalence of subclinical CHD and the role of SDB in mediating progression are not known. Information regarding the extent of subclinical disease in SDB participants and the progression of subclinical disease might provide evidence for use of noninvasively detected biomarkers of vascular disease as intermediate outcomes for assessing the role of SDB as a risk factor, as well as for assessing the impact of treatment of OSA on prevention of CHD.

### Sleep-Disordered Breathing and Heart Failure
- It is not clear how SDB affects the natural history of treated or untreated heart failure. Does treatment of OSA/CSA improve cardiac outcomes?
- Although after optimization of medical management small clinical studies have suggested a benefit for some treatment strategies, for example CPAP and/or supplemental oxygen, on CSA, larger randomized clinical trials are necessary to confirm these initial promising observations.

### Sleep-Disordered Breathing and Cardiac Arrhythmias
- The incidence and prevalence of arrhythmias in the setting of SDB is poorly defined. Studies to date have been small and have not had adequate control for potential confounders.
- The prognostic significance of arrhythmias occurring during SDB is unknown.
- It is not known whether treatment of SDB consistently decreases arrhythmias and favorably impacts cardiovascular mortality and morbidity.

### Gene–Environment Interactions
- Better characterization of the SDB/CVD phenotype is necessary.
• There is a need to identify genes common to SDB, CVD, and obesity.
• The extent to which SDB/OSA-related stressors may exacerbate cardiovascular disease, and the degree to which effects may vary in individuals with different underlying genetic susceptibility to cardiovascular disease is poorly understood.

Scientific Approaches
It was apparent to the workshop participants that many of the research questions posed could not be easily answered in the context of conventional clinical research. Thus, it was felt that there should be some priority given to encouraging the development of complementary basic science approaches (Figure 2). For example, the molecular mechanisms important in the pathophysiology of intermittent hypoxia might be best studied in tissue culture or murine models incorporating microarray, genomic, and proteomic techniques. Furthermore, approaches utilizing follow-up of children with SDB, who normally do not have other risk factors for CHD, may be uniquely informative. Such studies may provide clues to whether the SDB predicts the development of subsequent hypertension, metabolic syndrome, and endothelial dysfunction.

In order to address many of the epidemiological issues identified in the workshop, additional priority should be allocated to the development of new screening tools for the identification of SDB in large populations. Despite pioneering work performed by the SHHS,24 and the Wisconsin Sleep Cohort,25 full polysomnography is relatively burdensome and expensive for epidemiological research and clinical trial purposes. A number of less intrusive diagnostic techniques are available, but validation against polysomnography in large numbers of subjects is lacking. Assuming that current ongoing epidemiological studies will quantify the magnitude of “independent” risk conferred by SDB on the development of cardiovascular disease, such devices will be required to perform some of the additional prospective population-based studies recommended by workshop participants. These include verification of putative causal mechanisms and studies of intermediate outcomes in high-risk populations in which potential treatments can be evaluated. However, major large clinical intervention trials are premature at this stage pending more precise identification of SDB phenotypes, better understanding of causal mechanisms, and development of additional therapies that are both effective and well tolerated.

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Workshop Participants
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