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"DEPRESSION – AN ASTUTE VARIABLE IN PATIENTS WITH ACUTE CORONARY SYNDROME

Cardiology

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ABSTRACT

Introduction : The depression is common among patients who have an ACS with prevalence ranges from 16% to 23%. The rate is substantially higher than in the general population and primary care patients. Depression in cardiac patients is often both chronic and recurrent.
Despite its frequency, this psychiatric problem often go unrecognized and can persist for months to years, substantially impacting quality of life. In the setting of ACS, where great attention has been given to its frequent coexistence and prognostic import, rate of depression recognition is unknown.
Objective : To recognize incidence and prevalence of depression in ACS
Methods: All patients presenting with acute coronary syndrome were assessed for depression.
Conclusion : The study suggested that depressive symptoms should be included in the group of modifiable post-ACS risk factors that have a negative impact on patients quality of life and should therefore be considered in efforts to improve the health of these patients. Assessment of depressive symptoms in coronary patients should be performed independently of other cardiovascular risk factors, particularly in the elderly, men, and those who have the modifiable risk factors for cardiovascular disease.

KEYWORDS

Dexmedetomidine, Supratentorial tumour, Haemodynamics, Emergence reactions

INTRODUCTION

The term acute coronary syndrome (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and includes unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Each year in the United States, approximately 1.36 million people are hospitalized for ACS, of which 0.81 million are for myocardial infarction (MI) and the remainder are for UA. Roughly two-thirds of patients with MI have NSTEMI; the rest have STEMI, [1] of one third of STEMI patients die within 24 hours of onset of ischemia. [2] The morbidity and mortality is lower in UA/NSTEMI patients. [3] Almost 18% of men and 23% of women over age 40 may die within 1 year following MI. [4]

The depression is common among patients who have an ACS. Its prevalence ranges from 16% to 23%. [5, 6] This rate is substantially higher than that seen in the general population (4% to 5%) [7] or primary care patients (8% to 10%). [8] Rather than being a transient reaction to having cardiac disease, depression in cardiac patients is often both chronic and recurrent. [9,10] The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) [10] found that, among ACS patients who entered the hospital with major depression, 94% had been depressed for over one month, 61% had been depressed for over six months and more than half had a prior major depressive episode.

Furthermore, depressive symptoms are not transient after myocardial infarction, but instead persist if untreated. Two studies have found that depressive symptoms are essentially stable over the year following MI, with little reduction of symptoms over this period in untreated patients. Two pathways ("direct" and "indirect") are proposed which link the association of depression and ACS. "Direct" pathway refers to influences of depression on physiological factors that may lead to atherosclerosis or coronary events and consists of the autonomic imbalance and activation of the Hypothalamic Pituitary Axis, [11] depression leading to dysregulation of immunologic mechanisms (eg, proinflammatory cytokines such as interleukins [IL-1, IL-6] or tumor necrosis factor [TNF]), which are associated with an increased risk of CHD [12-14] and coagulation abnormalities and vascular endothelial dysfunction leading to the development or the progression of atherosclerosis in depressed people.[15-17]

Indirect pathways refer to psychosocial and behavioral mediators, which correlate with depression and CHD. Depression is associated with poor health behavior, maladaptive coping style, social isolation, and chronic life stress. [18] Behavioral risk factors such as smoking, low physical activity, poor diet and the failure to adhere to medical recommendations mediate the relationship of depressive disorders with CHD.

Depression has been independently associated with negative cardiac outcomes in patients with acute cardiac events and indeed, across the spectrum of cardiac disease. [19-22] Depression in healthy persons without cardiac disease have been associated with the development of coronary artery disease. Numerous studies of healthy men and women linking depression to the onset of cardiac illness; have found that depression was associated with a 60% increase in cardiac disease. [23]

Among patients with existing cardiac disease, depression has been associated with progression of the illness. Patients found to have depression when diagnosed with coronary artery disease are more likely to have acute cardiovascular/ischemic events than non-depressed patients [24] and hypertensive patients with depression are more likely to die of their cardiac disease. [25]

Given that current therapeutic modalities can effectively reduce depressive symptoms, its recognition as a co-morbidity in patients with ACS has the potential to improve patients' depression-related morbidity. [26] In fact, recent updates to the American College of Cardiology/American Heart Association guidelines recommend routine assessments of depressive symptoms so that appropriate interventions and follow-up can be instituted. However, in the setting of ACS, where great attention has been given to its frequent coexistence and prognostic import, rate of depression recognition is unknown.

There is lack of literature linking Depression and ACS in the Indian population , this study was undertaken to determine the prevalence of depression in ACS patients.

METHODS

A total of 100 patients presenting with acute coronary syndrome were enrolled in the study after informed consent.

The demographic and patient characteristics were collected and data on patient complaints, presenting illness and its duration were recorded. Risk factors like Hypertension, Dyslipidemia , Diabetes

Mellitus, Family history , Smoking and Alcohol were noted. Treatment history of any drugs for past psychiatric illness was also recorded.

Case definition of acute coronary syndrome [27]

1. **Myocardial infarction**

a. ST elevation MI (ECG)
b. Non ST elevation MI (Cardiac marker)

2. **Unstable angina**

a. Rest angina or angina with minimal exertion, usually lasting at least 20 minutes.
b. New onset severe angina, usually defined as occurring within the last month.
c. Crescendo angina, defined as previously diagnosed angina that has become distinctly more frequent, longer in duration or more severe in nature.

The **severity of depression** was measured by using **Hamilton Psychiatric Rating Scale For Depression** [28].

The scoring was done in the following manner :

0 – 50	: Total score
7 or less	: Normal
8 – 13	: Mild
14 – 18	: Moderate
19 – 22	: Severe
23 and above	: Very severe

STATISTICALANALYSIS:
All the information was collected using a structured proforma and entered in computer software. Crosschecking and data cleaning was done.

- Nominal data such as demographic data were presented as number and percentages.
- Continuous data (age, duration of disease, pulse BP) were expressed as mean, standard deviation and range.
- Chi-Square test was applied as appropriate for comparison of nominal data.
- P value of 0.05 was considered as statistically significant.

RESULTS
In our study, majority of patients were 40 to 70 years of age. Mean age of patients being 57.25 years, with a standard deviation of 10.38. We found that significantly high number of male patients were present(76% vs 24%) in our study group which was similar to Vural et al who had 82 patients with ACS (54 males and 28 females), mean age being 61.9±12.1 years [29-2].

The studies by ***Dias et al*** [29-30] and Yadav [31-32] also found significant male predominance with mean age of 59.4 and 56 years.

The major risk factors for ACS in the study group was alcoholism (43%) and Hypertension (43%), followed by DM (34%), smoking (34%) and hypercholesterolemia (33%). In a study by ***Yadav,*** tobacco consumption (65%) was a major risk factor followed by hypertension (33%), diabetes mellitus (16%), family history of coronary artery disease (14%) obesity (13%) and dyslipidemia (12%).

Frasure-Smith et al. demonstrated that depression is in itself an independent risk factor for cardiac events, particularly after infarction, patients with depression having a threefold increase in cardiac mortality, regardless of age and other risk factors.

Our study found that significantly high number of patients having ACS had depression (mild to severe) (37%), mean HAM-D score being 8.36 with a standard deviation of 5.54.

Bearing in mind that the prevalence of depression at some stage in life in the general population is estimated at 17%, these percentages may seem high, but the results are in agreement with data published from other studies that report major depression in 25 % of patients following myocardial infarction and symptoms of minor or major depression in 27 %-65%.

Amin et al [33] and Dias et al 29 found that the prevalence of moderate/severe depressive symptoms was 17.6% and 41.6% respectively.

Drago et al [34] showed that women had a higher prevalence of depression than men (35% vs 9%; p<0.01).

Amin et al [35] showed depressed patients were more likely to be younger, female, of a minority race, and to have a lower level of education as compared with nondepressed patients.

BMI and Depression:
Obesity and depression are interrelated health issues with numerous complications worldwide [35]. Our study found that the significantly high number of patients having ACS had high BMI (Overweight or obese). Mean BMI study group was 25.59 with standard deviation of 4.36. Our results are in the line with previous published literature.

However, none of the studies have assessed the association of BMI and depression in patients having ACS. We found that BMI and HAM-D score in our study group are correlated. The association is highly significant (p=0.032), indicating that in patients with ACS, HAM-D increases as BMI score increases. Our study is the first one to report the association of BMI and depression in patients having ACS.

We also found significant correlation between age and HAM-D score (p=0.000) which signifies as the age increases severity of depression increases, similar to the study by Dias et al [29] in which depressed patients were older than non-depressed patients (61.1 vs. 58.2 years, p = 0.06).

Risk factors and Depression:
Traditional risk factors have been identified in patients having ACS in multiple studies.

In our study with respect to association between ACS and depression , we found that the DM and hypercholesterolemia significantly affects the HAM –D score (p =0.000) however HT, alcohol and smoking does not affect the HAM –D score (p> 0.05).

These finding are similar to those reported in literature by Vural et al wich showed corelation between DM and hypercholestremia with depression.

Diabetes mellitus may place patients at risk for a depressive disorder through a biological mechanism linking the metabolic changes of this disease to changes in brain structure and function 36. Use of serotoninergic antidepressants (e.g., fluoxetine) to treat depression in diabetics has been found to reduce hyperglycemia, normalize glucose homeostasis, and increase insulin sensitivity37. Therefore, the relationship between depression and diabetes mellitus is a bidirectional phenomenon. We believe that diabetes mellitus may also be regarded as a risk factor for depression and anxiety disorder following ACS

As our findings indicated that a relationship exists between hypercho lesterolemia and depression scores, however, we do not know the exact mechanism of this phenomenon. Many studies have investigated this association. Ledochowski et al.[38] showed that hypercholesterolemia may not necessarily increase the risk of depressive mood; conversely, increased intake of fat and carboh ydrates by individuals with depressive mood may increase cholesterol levels. There are also controversies surrounding the possible relationship between hyperch olesterolemia and depression[39].

One study has indicated that long-term cholesterol lowering therapy has different effects on serotonin transmission. This finding suggests that within this period some patients could be vulnerable to depression, violence, or suicide[40].

DISCUSSION
ACUTE CORONARY SYNDROME
The term *acute coronary syndrome* (ACS) refers to any group of clinical symptoms compatible with acute myocardial ischemia and covers the spectrum of clinical conditions ranging from unstable angina (UA) to non– ST-segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). [41]

Incidence and prevalence:
Men are slightly more likely to have cardiac illness than female. Age over 45 years for men and 55 years for women, family history of cardiovascular disease and modifiable risk factors like hypertension,

hyperlipidemia, diabetes, sedentary lifestyle, and smoking are alarming for developing ACS.

In addition to these risk factors, it has become increasingly clear that psychological factors, particularly depression, may play an important role in the development and propagation of cardiac disease. Depression is common in patients with acute coronary syndrome and is independently prognostic of a higher mortality and worse health status. Depression has been implicated in both the onset and outcome of acute coronary syndromes.

The prevalence of major depression ranges from 15% to 23%, [42] which is approximately threefold higher than age-matched, community-based prevalence studies.[42,43] Recovery from depression associated with ACS is extremely poor, with many patients remaining depressed months later.[44,45] Moreover, women generally experience greater depressive symptomatology following ACS than men do,45-47 and this symptomatology may more detrimentally affect their prognosis and quality of life.[48-49]Also untreated depression results in a poorer prognosis for patients with cardiovascular problems. [50]

Data from the Heart and Soul Study, a cross-sectional survey of 1024 people with CAD (coronary artery disease) revealed that those with depressive symptoms not only had increased risk of all-cause mortality, but also were more likely to report worse symptom burden, disease-specific quality of life, physical limitations, and overall health.51-52 Therefore it is not surprising that patients with CAD and depression have higher overall medical costs compared with similar patients without depression. [53-54]

Studies in patients without known CAD have demonstrated that depression is linked to an increased risk of developing CAD. [55] For example, a cohort of 81,875 patients from the Nurses' Health Study showed that specifically in women with no previous history of CAD, there was a statistically significant age-adjusted trend for the association of increasingly more severe depression scores with fatal CAD, myocardial infarction, and sudden cardiac death.[56]

Finally, patients with both CAD and depression have demonstrated lower adherence with treatment, diet and exercise, and smoking cessation, all of which can contribute to the negative consequences of depression in this population.[57-58]Recently, the impact of such negative behaviors in this population was further elucidated by the Heart and Soul Study investigators, who found a significant relationship between physical inactivity and cardiovascular events when adjusting for a number of variables including comorbid conditions, depression severity, smoking, and drug therapy compliance. [52]

Though some cardiac illnesses may have associated impairments of appetite, concentration, sleep, and energy, true depression (with persistent depressed mood or anhedonia) is not a normal consequence of cardiac disease. Rather than being a transient reaction to having cardiac disease, depression in cardiac patients is often both chronic and recurrent. [59]

The large **Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) trial 60** found that, among ACS patients who entered the hospital with major depression, 94% of such patients had been depressed for over one month, 61% had been depressed for over six months and more than half had a prior major depressive episode. Furthermore, depressive symptoms are not transient after myocardial infarction, but instead persist if untreated.

The ***Johns Hopkins*** Precursor study followed male medical students for 40 years and found depression to independently predict the subsequent development of cardiac disease and MI. Since that time, there have been numerous studies of healthy men and women linking depression to the onset of cardiac illness; a meta-analysis of this population found that depression was associated with a 60% increase in cardiac disease.[61]

Among patients with existing cardiac disease, depression has been associated with progression of the illness. Patients found to have depression when diagnosed with coronary artery disease at cardiac catheterization are more likely to have acute cardiovascular/ischemic events than nondepressed patients and hypertensive patients with depression more likely to die of their cardiac disease. Also, patients with depression in the setting of acute myocardial ischemia (ACS) have substantially impaired medical/cardiac outcomes compared to those without depression.

One of the largest international case control studies ever performed with the aim of identifying the risk factors associated with coronary disease- **the INTERHEART study** - demonstrated that more than 90% of the overall risk for MI can be predicted on the basis of 9 risk factors. Psychosocial variables including stress and depression were important predictors of risk for MI (odds ratio [OR] 2.67; 99 % confidence interval 2.21-3.22) in all age-groups, countries and ethnic groups, their effect being comparable to that of hypertension or abdominal fat. If this relationship is truly causal, it is much more important that previously thought, and a substantial proportion of MIs can be attributed to such factors.

A recent longitudinal study of post- ACS depression found that baseline depression severity a few weeks after ACS was a strong and independent risk factor for cardiac mortality approximately 7 years after the index event. Findings from this study and others indicate that ACS patients whose depression is resistant to standard treatments appear to be at highest risk of suffering adverse cardiac outcomes. 62 It is unclear whether this is because the depression persists or whether this is a separate subtype of depression.

In addition to the long-term effects of post-ACS depression, it appears that depression may also have immediate detrimental effects among those admitted to the hospital with acute myocardial ischemia. In this regard, at least two studies have found that MI patients who enter the hospital with an ongoing major depressive episode are more likely to have an in-hospital cardiac complication.63 Though most studies of ACS patients have primarily evaluated depression after MI, depression in the setting of UA has also been specifically associated with cardiac morbidity and mortality.

Mechanisms linking depression and myocardial ischemia:

Overall, there are two mechanistic categories that likely contribute to link depression and myocardial ishemia: physiologic effects and behavioral effects. (Figure 2)

Physiologic effects of depression have shown its corelation with platelet hyperreactivity and aggregation mediated by serotonin [64], elevations of other inflammatory markers (eg, IL-1, IL-6, and TNF-α) [65,] diminished HRV [66], sympathetic nervous system dysregulation 67, Endothelial dysfunction[68].

Following studies assessed the impact of depression after a cardiac event. It is seen that the depression as having a negative influence on outcome criteria such as cardiac morbidity, cardiac mortality, or total mortality. (Figure[3,4,5])

Hamilton Rating Scale for Depression:

The **Hamilton Rating Scale for Depression (HRSD)**, also known as the **Hamilton Depression Rating Scale (HDRS)** or abbreviated to **HAM-D**, is a multiple choice questionnaire that clinicians may use to rate the severity of a patient's major depression.[69] Max Hamilton originally published the scale in 1960 [70] and reviewed and evaluated it in 1966[71], 1967 [72], 1969 [73,] and 1980[74].

The questionnaire rates the severity of symptoms observed in depression such as low mood, insomnia, agitation, anxiety and weight loss. The questionnaire is presently one of the most commonly used scales for rating depression in medical research.

Unlike other depression measures, the *Hamilton Rating Scale* for *Depression* was developed in a medical setting and, for more than 30 years, used concurrently with antidepressant medication to evaluate treatment response.

Description of the Rating Scale

The variables are measured either on five-point or three-point scales, the latter being used where quantification of the variable is either difficult or impossible. No distinction is made between intensity and frequency of symptom, the rater having to give due weight to both of them in making his judgment. Various problems are to be found with specific symptoms. Thus considerable difficulty is found with the depressive triad: depressive mood, guilt, and suicidal tendencies. These are so closely linked in description and judgment as to be very difficult to separate. It is very important to avoid the halo effect by

automatically giving all of them high or low scores, as the case may be.

Depressed Mood-This tends to have a narrow range of scores, for no diagnosed patients will score zero and few will score 1 or 4. The most useful indicator for depressed mood is the tendency to weep, but it must always be considered against the cultural background, and patients may also "go beyond weeping".

Suicide-An attempt at suicide scores 4, but such an attempt may sometimes occur suddenly against a background of very little suicidal tendency; in such cases it should be scored as 3. There will be great difficulty sometimes in differentiating between a real attempt at suicide and a demonstrative attempt; the rater must use his judgment.

Work and Loss of Interest-Difficulties at work and loss of interest in hobbies and social activities are both included. The patient who has given up work solely because of his illness is rated 4.

Retardation-A grade 4 patient is completely mute, and is therefore unsuitable for rating on the scale. Grade 3 patients need much care and patience to rate, but it can be done.

Agitation-This is defined as restlessness associated with anxiety. Unfortunately, a five-point scale was found impracticable, and therefore this variable is rated on a three-point scale. The mildest degrees of agitation cause considerable difficulty.

Gastro-intestinal Symptoms-These occur in connexion with both anxiety and depression. Considerable clinical experience is required to evaluate them satisfactorily. The definitions given have been found very useful in practice.

General Somatic Symptoms-In depressions these are charact eristically vague and ill defined, and it is extremely difficult to get a satisfactory description of them from the patient.

Hypochondriasis-This is easy to rate when it is obviously present, but difficulties arise with mild hypochondriacal preoccupations. Phobias of specific disease can cause difficulties. A phobia of venereal disease or of cancer will sometimes be rated under "guilt" by the nature of the symptom, but other cases may give rise to much doubt and judgment requires care. Fortunately, phobias are not common, but the whole subject of Hypochondriasis could well repay clinical investigation.

Insight-This must always be considered in relation to the patient's thinking and background of knowledge. It is important to distinguish between a patient who has no insight and one who is reluctant to admit that he is "mental".

Loss of Weight- Ideally this would be measured in pounds or kilograms, but few patients know their normal weight and keep a check on it. It was therefore necessary to use a three point scale. After recovery from depression, some patients sometimes show a brief hypomanic reaction, during which the exuberantly cheerful patient will deny that he has any symptoms whatever, though he is obviously not to be regarded as normal. In such cases, the rating scale is inapplicable and should be delayed until the patient has fully recovered.

Scoring: It is particularly useful to have two raters independently scoring a patient at the same interview, since this gives data for calculating the interphysician reliability. The score for the patient is obtained by summing the scores of the two physicians. This is, of course, the best way of learning how to use the scale, where only one rater uses the scale; the scores should be doubled so as to make them comparable. With sufficient experience, a skilled rater can learn to give half-points.

CONCLUSION

Depression is common after hospitalization for acute coronary syndrome, particularly in men, and is mainly linked to pre-hospitalization factors (BMI, DM, hypercholesterolemia). DM and hypercholesterolemia significantly affects the depression ($p < 0.05$) however HT, alcohol and smoking does not affect the depression ($p > 0.05$). This study is one of the first one to report the association of BMI, DM, hypercholesterolemia and depression in patients having ACS.

The study also suggested that depressive symptoms should be included in the group of modifiable post-ACS risk factors that have a negative impact on patients' quality of life and should therefore be considered in efforts to improve the health of these patients. Assessment of depressive symptoms in coronary patients should be performed independently of other cardiovascular risk factors, particularly in the elderly, men, and those who have the risk factors (DM, hypercholesterolemia etc.) The large prospective studies are required to substantiate the fact of our study.

ACKNOWLEDGEMENT:

None

CONFLICT OF INTEREST

No conflict of interest

ETHICAL APPROVAL

Ethical clearance was obtained by the respective institution.

Table 1 :**Body Mass Index (BMI)**[32] was calculated as weight (kg) divided by height in meters squared (m^2).

Table 1	BMI (kg/m2)
Underweight	<18.5
Healthy weight	18.5-24.9
Overweight	25.0-29.9
Obesity	30.0-34.9
Obesity	35.0-39.9
Extreme Obesity	≥40

Table 2: HYPERTENSION based on JNC 7 CLASSIFICATION

Table 2 :Blood pressure classification	Systolic, mmHg	Diastolic mmHg
Normal	< 120	And < 80
Prehypertension	120- 139	Or 80 -89
Stage 1	140 – 159	Or 90-99
Stage 2	≥160	Or ≥100
Isolated systolic hypertension	≥140	And < 90

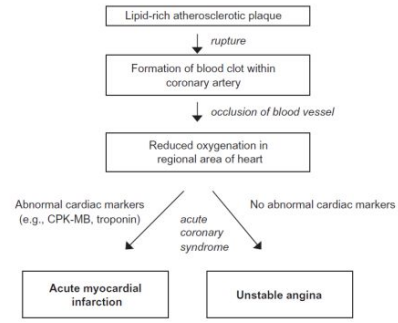

Figure 1: *Pathophysiology of acute coronary syndrome*
The figure shows the pathophysiology of acute coronary syndrome leading to acute myocardial infarction or unstable angina . (CPK-MB: Creatine kinase –MB)

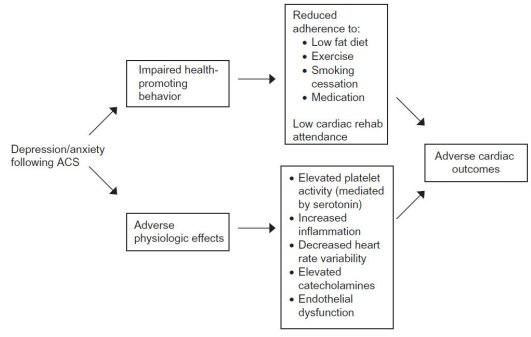

Figure 2: *Putative mechanisms linking depression/anxiety and cardiac outcomes in acute coronary syndrome (ACS) patients.*
The figure represents the various mechanisms linking the correlation between depression and acute coronary syndrome .

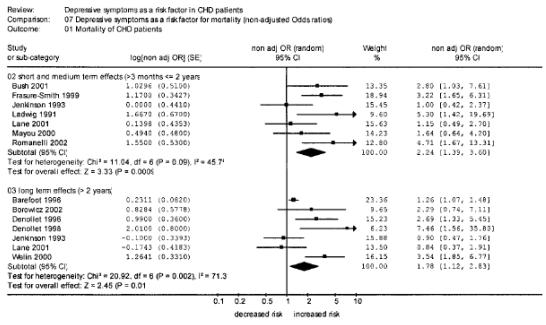

Figure 3: *Depressive symptoms as a risk factor for mortality (univariate risk estimates using odds ratios).*

The figure explains the odds ratio of depression as a univariate variable as a risk factor for mortality in coronary heart disease patients. (CHD: coronary heart disease), (OD: Odds ratio)

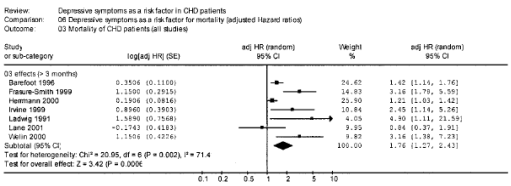

Figure 4: *Depressive symptoms as a risk factor for mortality (adjusted risk estimates using hazard ratios).*

The figure explains depression as adjusted risk factor for mortality in coronary heart disease patients. (CHD: coronary heart disease), (HR: Hazards ratio)

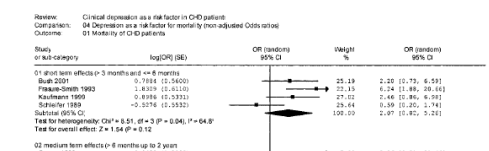

Figure 5: *Clinical depression as a risk factor for mortality (univariate risk estimates using odds ratios).*

The figure explains the univariate analysis of clinical depression as a major adjusted risk factor for mortality in coronary heart disease patients , hence proving the need for treatment of depression . (CHD: coronary heart disease)

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