# PREVALENCE OF HYPERHOMOCYSTEINEMIA IN PATIENTS WITH ACUTE CORONARY SYNDROME

A dissertation

Submitted to the Iraqi Board for Medical Specializations in partial fulfillment for the degree of the fellowship in Medicine

By

**Ammar Salih Abood**

**MBChB**

Supervisor

**Dr.Abdulraheem Alhumrani**
**MBChB, CABM**

Professor of Medicine, Department of Medicine,
Basrah College of Medicine, University of Basrah

# Abstract

**Background:** Hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular disease and for recurrent venous thromboembolism.

Homocysteine has primary atherogenic and prothrombotic properties. There is relationship between elevated blood homocysteine concentrations and coronary heart disease (CHD), which appear to be associated with an increased risk of cardiovascular and cerebrovascular disease.

**Aims of the study:**

1) To estimate the prevalence of hyperhomocysteinemia among patients with acute coronary syndrome.

2) To compare the level of hyperhomocysteinemia among patients with different forms of acute coronary syndrome, i.e. STEMI, NSTEMI, and Unstable Angina.

3) To explore the relationship of hyperhomocysteinemia with other risk factors for CHD such as smoking, hypertension, and diabetes.

**Methods:** A total of 130 patients, **77** males with age range **(26-75 years)** with mean **(52.20± 10.41)** and **53**females with age range **(20-71 years)** with mean **(53.47±8.77)** were included in 16 month study conducted from 4$^{th}$ September 2011 to 15$^{th}$ January 2013 in Basrah General Hospital Coronary Care Unit Fasting blood sample was withdrawn from the patients and Homocysteine level was measured with lipid profile, blood glucose, blood urea, serum creatinine, serum troponin titer. The cut off value for homocysteine 15 **µmol/L**.

**Result:** The prevalence of hyperhomocysteinemia was (44.6%) patients {39 (50.6%) male and 19(35.8%) female} but the difference was statistically not significant (p> 0.05).STEMI is more common in young adults aged 20-40 years. NSTEMI is more common in old patients (61 years and above) while unstable

angina is more frequent in middle aged persons(41-60 years),with this variation being significant ($p<0.05$).The study showed an association between smoking and serum homocysteine level; this is evident by 44(57.1%) smoker patients have hyperhomocysteinemia and 33(42.9%) smokers have normal serum homocysteine level, this relationship is statistically significant as the p value 0.001.

## Conclusion:

Hyperhomocysteinemia is prevalent in patients with acute coronary syndrome as (44.6%) of the patients had high serum homocysteine level.

The level of homocysteine seems significantly related to smoking as (57.1%) of the smokers had hyperhomocysteinemia.

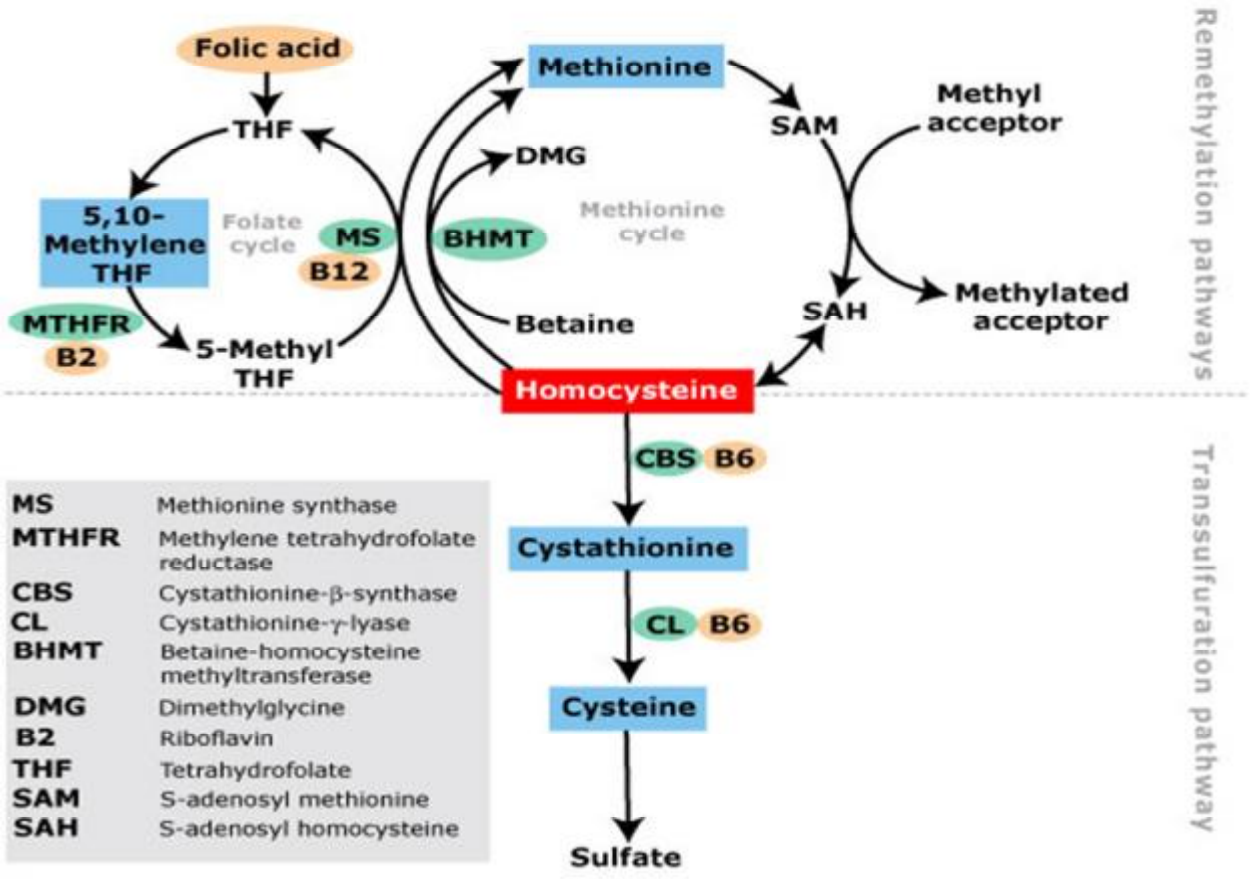
No significant variation in serum homocysteine level was found among different subtypes of ACS.

Hyperhomocysteinemia was not found to be significantly related to hypertension and diabetes.

# Introduction

Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. Homocystinuria or severe hyperhomocysteinemia is a rare autosomal recessive disorder characterized by severe elevations in plasma and urine Homocysteine concentrations. Clinical manifestations of homocystinuria include developmental delay, osteoporosis, ocular abnormalities, thromboembolic disease, and severe premature atherosclerosis. [1]

Less marked elevations in plasma Homocysteine are much more common, occurring in 5 to 7 percent of the population [1]. Although unassociated with the clinical stigmata of homocystinuria, mounting evidence suggests that moderate Hyperhomocysteinemia is an independent risk factor for atherosclerotic vascular disease and for recurrent venous thromboembolism. [1]



## AETIOLOGY OF HYPERHOMOCYSTEINEMIA

Homocysteine is metabolized by one of two divergent pathways: transsulfuration and remethylation .The transsulfuration of homocysteine to cysteine is catalyzed by cystathionine-ß-synthase, a process that requires pyridoxal phosphate (vitamin B6) as a cofactor. Remethylation of homocysteine produces methionine. This reaction is catalyzed either by methionine synthase or by betaine-homocysteine methyltransferase. Vitamin B12 (cobalamin) is the precursor of methylcobalamin, which is the cofactor for methionine synthase.[2]

Elevations in the plasma homocysteine concentration can occur due to genetic defects in the enzymes involved in homocysteine metabolism, to nutritional deficiencies in vitamin cofactors, or to other factors including some chronic medical conditions and drugs [3]. Some drugs used in the treatment of hypercholesterolemia, such as fibrates and nicotinic acid, can raise homocysteine levels by approximately 30 percent; however, the clinical significance of this is uncertain [4-5]. Cigarette smoking also may elevate homocysteine levels [6]. Chronic kidney failure can increase homocysteine levels due to decreased renal removal and impaired metabolism.[3]

**Thermolabile variant of methylene tetrahydrofolate reductase** — The most common form of genetic hyperhomocysteinemia results from production of a thermolabile variant of methylene tetrahydrofolate reductase (MTHFR) with reduced enzymatic activity (T mutation)[7]. The gene encoding for this variant contains a cytosine to thymine substitution at nucleotide 677 (C677T) [8].

The responsible gene is common, with a population frequency estimated between 5 to 14 percent [9]. Homozygosity for the thermolabile variant of MTHFR (TT genotype) is a relatively common cause of mildly elevated plasma homocysteine levels in the general population, often occurring in association with low serum folate levels [10,11].

As an example, one study of 625 men found that 11.5 percent were homozygous for the TT genotype [10]. However, for those in the top 5 and 10 percent of plasma homocysteine concentrations, the frequency rose to 48 and 36 percent, respectively. Homozygotes also had the lowest serum folate concentrations.

**Vitamin deficiencies** — Increased blood levels of homocysteine may reflect deficiency of folate, vitamin B6, and/or vitamin B12[12]. Plasma folate and B12 levels, in particular, are strong determinants of the homocysteine concentration. Homocysteine levels are inversely related to folate consumption, reaching a stable baseline level when folate intake exceeds 400 µg/day [13]. Vitamin B6 is a weaker determinant [13].

The importance of vitamin deficiency in the pathogenesis of hyperhomocysteinemia was evaluated in a cohort of 1041 elderly subjects. Two-thirds of patients with elevated homocysteine levels had a subnormal plasma concentration of folate, vitamin B12, or pyridoxal-5-phosphate (the coenzyme form of vitamin B6). The prevalence of low plasma B12 levels was higher in this cohort than in the younger participants in a European case-control study [13]. These data suggest that suboptimal B12 intake coupled with poorer absorption might play a greater role in elevating homocysteine and subsequent CHD risk in older adults than in younger patients. In contrast, folate intake low enough to raise plasma homocysteine may be relatively common in the general population, particularly in moderate consumers of alcohol.

Further evidence of the importance of vitamin deficiency comes from a report that assessed the results of the United States Food and Drug Administration regulation requiring all enriched grain products be fortified with folic acid. Patients who had blood tested following fortification had significantly higher blood folate concentrations and lower homocysteine concentrations [14].

In addition, the prevalence of a high homocysteine concentration (>13 µmol/L) decreased from 18.7 before fortification to 9.8 percent after fortification.

Additional support for the role of folic acid and perhaps vitamin B6 in hyperhomocysteinemia comes from a trial that randomly assigned 158 healthy siblings of 167 patients with premature atherothrombotic disease to folic acid (5 mg daily) and vitamin B6 (250 mg daily) or placebo; most of the siblings and all of the patients had postmethionine loading hyperhomocysteinemia. After a two-year follow-up, fasting and postmethionine homocysteine levels significantly decreased with vitamin supplementation, from 14.7 to 7.4 µmol/L and 64.9 to 34.9 µmol/L respectively, while there were no changes with placebo therapy.[14]

**ATHEROTHROMBOTIC PROPERTIES OF HOMOCYSTEINE** — Homocysteine has primary atherogenic and prothrombotic properties. Histopathologic hallmarks of homocysteine-induced vascular injury include intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation, and the formation of platelet-enriched occlusive thrombi [15]. These observations may help explain the association between hyperhomocysteinemia and cardiovascular disease described below.

There are multiple mechanisms by which homocysteine may induce vascular injury:

- Homocysteine promotes leukocyte recruitment by upregulating monocyte chemoattractant protein-1 and interleukin-8 expression and secretion [16].
- The thiolactone metabolite of homocysteine can combine with LDL-cholesterol to produce aggregates that are taken up by vascular macrophages in the arterial intima; these foam cells may then release the lipid into atherosclerotic plaques.
-

- Homocysteine increases smooth muscle cell proliferation and enhances collagen production [17].
- Prothrombotic effects of homocysteine, which have been demonstrated in patients with acute coronary syndromes [18], include attenuation of endothelial cell tissue plasminogen activator binding sites, activation of factor VIIa and V, inhibition of protein C and heparin sulfate, increased fibrinopeptide A and prothrombin fragments 1 and 2, increased blood viscosity, and decreased endothelial antithrombotic activity due to changes in thrombomodulin function[19].
- Oxidative stress by free radicals formed during the oxidation of reduced homocysteine may directly injure endothelial cells[20].
- Marked platelet accumulation may be secondary to direct proaggregatory effects of homocysteine or to an impairment in endothelium-mediated platelet inhibition [21].
- Prolonged exposure of endothelial cells to homocysteine reduces the activity of dimethylarginine dimethylaminohydrolase, the enzyme that degrades asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase; this impairs the production of nitric oxide [21,22]. This may contribute to impaired endothelium-dependent vasodilation of both conduit and resistance vessels [23].

Support for the role of homocysteine in endothelial dysfunction is derived from studies that found that folic acid supplementation both lowers the homocysteine concentration and improves measures of endothelial dysfunction [24].

An alternate view is that hyperhomocysteinemia is not directly harmful, but that it indirectly inhibits methyl fluxes during transmethylation of methionine; the resulting impairment of DNA methylation could then affect many physiologic processes [25].

A study in patients with uremia and hyperhomocysteinemia found increased levels of DNA hypomethylation and altered gene expression that were corrected by administration of folate [26].

**LABORATORY DIAGNOSIS** — Sensitive assays allow quantification of the total plasma homocysteine concentration; approximately 75 to 85 percent is protein-bound and 15 to 25 percent is in acid-soluble free forms [27]. Normal homocysteine concentrations range between 5 and 15 µmol/L. Hyperhomocysteinemia has been classified as follows [28]:

- Mild (15 to 30 µmol/L)
- Moderate (30 to 100 µmol/L)
- Severe (>100 µmol/L)

An oral methionine challenge (100 mg/kg) can be given to patients suspected of hyperhomocysteinemia who have normal fasting homocysteine levels [29]. The oral methionine challenge is more useful for patients with cystathione-beta-synthase deficiency than for those MTHFR reductase deficiency [9]. The homocysteine concentration is measured on fasting samples before the methionine challenge and four and eight hours afterward. The patient is classified as having impaired homocysteine metabolism if the four hour post-methionine plasma homocysteine concentration exceeds the appropriate mean level by more than two standard deviations.

However, the prognostic significance of the oral methionine challenge is uncertain. In one series that included 24 of 163 subjects with homozygosity for the thermolabile variant, fasting but not postmethionine total homocysteine levels were associated with CHD status [9].

Homocysteine levels measured at the time of admission for acute myocardial infarction and unstable angina appear to be accurate [30].

In this small study, levels at admission were similar to those six months after the acute event, but there were minor variations in the homocysteine level during the first week after admission.

## Role in Vascular Disease

**Hyperhomocysteinemia** — Although early data on the relationship between elevated blood homocysteine concentrations and coronary heart disease (CHD) and stroke have been somewhat inconsistent [31-33], high homocysteine levels appear to be clearly associated with an increased risk of cardiovascular and cerebrovascular disease. However, homocysteine does not appear to be as important as other risk factors such as hypercholesterolemia, smoking, diabetes mellitus, and hypertension.

A meta-analysis that evaluated data from 30 prospective and retrospective studies, involving 5073 ischemic heart disease and 1113 stroke events, provides an analysis of the varied data [34]. Stronger associations between the blood homocysteine concentration and cardiovascular events were noted in retrospective compared with prospective studies. After adjustment for known cardiovascular risk factors, a 25 percent lower homocysteine concentration (about 3 µmol/L) in the prospective studies was associated with a lower risk of ischemic heart disease risk (odds ratio 0.89, 95% CI 0.83-0.86) and stroke (odds ratio 0.81, 95% CI 0.69-0.95).

These results are supported by a meta-analysis of 40 observational studies involving 11,162 patients who were homozygous for the thermolabile variant of MTHFR and 12,758 matched controls [35]. Patients with the MTHFR TT genotype had a 16 percent higher odds of coronary heart disease compared with controls (odds ratio 1.16, 95% CI 1.05-1.28). Additionally, the MTHFR TT genotype is associated with an increased risk of silent brain infarcts [36].

A meta-analysis performed for the US Preventive Services Task Force specifically examined the issue of whether homocysteine levels add predictive value for determining the risk of CHD in adults without known CHD [37].

The analysis found that, independent of Framingham risk factors, each increase in homocysteine level of 5 µmol/L increases the risk of CHD events by approximately 20 percent.

Hyperhomocysteinemia has been linked to the following vascular events:

- Myocardial infarction, other acute coronary syndromes, and recurrent coronary events [39,41]
- Premature coronary heart disease [42]
- Cardiovascular and total mortality [41,43]
- Adverse outcomes after angioplasty [45]
- Carotid artery stenosis [46]
- Stroke [47], recurrent stroke [48], and silent brain infarct [49]

Homocysteine levels have also been linked to the development of heart failure. A community-based cohort study found that higher homocysteine levels increased the risk of heart failure even after controlling for interim myocardial infarctions [51].

The issue of whether homocysteine plays a causal role in cardiovascular disease or whether there is a non-causal association has additionally been addressed by meta-analyses that have looked at both prospective studies and MTHFR mutation studies [51,52]. Similar odds ratios for cardiovascular disease were found in both types of studies. The consistent odds ratios across studies that should have had distinct sources of bias and error argue in favor of a causal role for Homocysteine [53].

# AIMS OF THE STUDY:

1) To estimate the prevalence of Hyperhomocysteinemia among patients with acute coronary syndrome.
2) To compare the level of Hyperhomocysteinemia among patients with different forms of acute coronary syndrome, i.e. STEMI, NSTEMI, Unstable Angina.
3) To explore the relationship of hyperhomocysteinemia with other risk factors for CHD such as smoking, hypertension, and diabetes.

# PATIENT AND METHODS:

This is Cross Sectional study which involved a total of 130 patients, **77** males and 53females were included in 16 months study conducted from 4th September 2011 to 15th January 2013 in Basrah General Hospital Coronary Care Unit.

# INCLUSION CRITERIA:

Patients included in this study were those who were admitted to the coronary care unit in Basrah General Hospital and diagnosed as Acute Coronary Syndrome according to the European Society of Cardiology (ESC) and American Heart Association (AHA).[57]

Any patient who was admitted to the C.C.U. evaluated and categorized according to the clinical presentation and electrocardiographic finding and cardiac enzyme (characteristically serum Troponin I titre) into

1) ST Segment Elevation Myocardial Infarction.

2) Non ST segment Elevation Myocardial Infarction.

3) Unstable Angina.

Complete history was taken and physical examination performed, twelve standards leads ECG was done and investigations in form of (fasting blood sugar, blood Urea, Serum creatinine, serum cholesterol, serum triglyceride, serum low density lipoprotein, serum high density lipoprotein, serum Troponin level, Hemoglobin) were requested. Fasting Homocysteine level was measured on day 2 of admission.

**EXCLUSION CRITERIA:**

Patients on drugs like methotrexate, carbamazapine, phenytoin, levodopa, vitamin B6, B12, folic acid, patients with known malignancy like Acute Leukemia, carcinoma of breast, pancreas or ovary; known chronic liver disease patients; also patients with GFR less than 50% and known hypothyroid patients.

## Procedure:

Homocysteine assay performed by Diazyme Homocysteine Smart Assay kit supplied from Diazyme Laboratories, California, USA, by specialist biochemist.

## Principle:

Diazyme Homocysteine assay principle based on the method in which oxidized homocysteine (Hcy) is first reduced to free homocysteine (Hcy_) which then react with co-substance, S-adenosylmethionine (SAM) catalyzed by a Hcy S- methyl transferase to form methoinine ( Met) and S – Adenosyl homocysteine (SAH). SAH is assessed by coupled enzyme reactions including SAH hydrolase, adenosine deaminase (Ado) and glutamate dehydrogenase, wherein SAH is hydrolyzed into adenosine and homocysteine (Hcy) by SAH hydrolyase. The formed Hcy that is originated from co –substrate SAM is cycled into Hcy conversion reaction by Hcy S – methyltransferase. This forms a co – substrate conversion product = based enzyme cycling reaction system with significant amplification of detecting signals. The formed Ado is immediately hydrolyzed into inosine and ammonia which reacts with glutamate dehydrogenase with concomitant conversion of NADH to $NAD^+$. The concentration of Hcy in the sample is indirectly proportional to amount of NADH converted to NAD and absorbance will be measured by SMART Eurolyser photometer at 340nm.

## Reference range: < 15 µmol/L

## Statistical Analysis:

The data were analyzed in the computer by using SPSS ( Statistical Package for Social Science) version 17, and the results were presented into simple self explanatory tabulation. The test used was Chi-square test to show significance. P value of less than 0.05 was considered significant.

# RESULT:

The study revealed that out of the total of 130 patients, 77 (59.2%) were males whose ages ranged between (26-75 years) with a mean of (52.2± 10.4) and 53(40.8%) were females whose ages ranged between (20-71 years) with a mean of (53.5±8.8 ). Ninety(69.2%) of the patients were the age range(41-60 years) as shown in Table 1. The mean homocysteine level of the patient (13.1 ± 11.4) µmol/L.

This study showed that 83(63.8%) patients had got STEMI, 41(31.5%) patients with NSTEMI and 6(4.6%) with unstable angina. The also shows that 51(66.2%) of the males and 32(60.4%) of the females got STEMI, 23(29.9%) of the males and 18(34%) of the females got NSTEMI and 3(3.9%) males and 3(5.7%) females got unstable angina as shown in Table 2. The overall distribution of ACS subtypes with gender was not significant ($p>0.05$).

Table 3 showed the distribution of ACS subtypes by age. STEMI is more common in young adult aged 20-40 years. NSTEMI is more common in old patients (61 years and above) while unstable angina is more frequent in middle aged person (41-60 years).with this variation being significant ($p<0.05$).

Also, the results showed that the prevalence of hyperhomocysteinemia was (44.6%) patients {39 (50.6%) male and 19(35.8%) female} but the difference was statistically not significant ($p> 0.05$) as shown in Table 4.

In addition the study showed that 10 (71.4%) patients from the total 14 patients with in the age range 20-40 years have hyperhomocysteinemia, 32(35.6%) patients from the total of 90 patients with in the age range 41-60 years, and 16(61.5%) patients from the total 26 patients age 61-80 years. The relationship is statistically significant, the p value 0.006(<0.05), as shown in table 5.

The study also showed that there is no significant relation between high serum homocysteine level and the incidence of acute coronary syndrome which is evident by 44.6% hyperhomocysteinemic patients from the total of 130 patients versus 55.4% with normal homocysteine level, furthermore no significant difference was found in the homocysteine level and various presentation of acute coronary syndrome i.e. STEMI, NSTEMI, UA, as shown in table 6

It also showed association between smoking and serum homocysteine level; this is evident by 44(57.1%) smoker patients have hyperhomocysteinemia and 33(42.9%) smokers have normal serum homocysteine level. this relationship is statistically significant as the p value 0.001 (<0.05), as shown in table 7..

The study verified that there no significant relationship between serum homocysteine level and hypertension as evident by only 34(47.2%) of the hypertensive patient have Hyperhomocysteinemia, while 38 (52.8%) patients have normal Homocysteine level i.e. the p value 0.5 which is statistically not significant, as shown in table 8.

No significant relation was noticed between diabetes and homocysteine level because only 18(39.1%) of the diabetic patient included in the study had elevated serum Homocysteine in comparison to 28 (60.9% ) with normal Homocysteine level, the p value 0.35, as shown in table 9.

To explore the relative importance of predictors of hyperhomocysteinemia we use logistic regression analysis in which hyperhomocysteinemia versus normal level was the dependent variable. The independent variables were age, sex, smoking, hypertension, and diabetes. None was a significant predictor.

# Discussion:

The result of our study show that the frequency of hyperhomocysteinemia is more in the age group less than 60 years (p value 0.006) this finding is consistent with a case control study in Tufts University,concerning the Prevalence of familial Hyperhomocysteinemia in men with premature coronary artery disease < 60 years which enrolled 176 male patient with premature CAD confirmed angiographically with 250 healthy controls, the result showed significant relation with hyperhomocysteinemia and CAD, p value 0.001 which is consistent with our finding .[42]

Other finding is the significant association between smoking and hyperhomocysteinemia with P value 0.001 which is consistent with a study in Tulane University which studied the relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. There were positive and significant dose-response relationships between measures of cigarette smoking (cigarettes per day, pack-years, and serum nicotine levels) and elevated levels of novel risk factors. The findings suggest that inflammation and Hyperhomocysteinemia may be important mechanisms by which smoking promotes atherosclerotic disease, the relation with Homocysteine is significant (P<0.001).[6]This study shows that there is no association between hypertension and hyperhomocysteinemia, this finding is inconsistent with other studies like case control study in Griffith University which involved 250 hypertensive patients and 250 age, sex and racially matched normotensive controls to assess the relationship between Homocysteine and gene variant (C677T) as a risk factor for essential hypertension .Comparison of C677T allele frequencies revealed a higher proportion of the mutant allele (T) in the EH group (40%) compared to unaffected controls (34%) (p=0.07).

Furthermore, genotypic results indicated that the prevalence of the homozygous mutant genotype (T/T) in the affected group was higher than that of controls (14%:10%) (p=0.17)[55].

This result is inconsistent with our result as the p value 0.5 as shown in table 8.we think this is because relatively small sample size and the absence of control group, in addition the above study involve gene study by PCR and oral methionin load to detect borderline cases.

In addition this study shows no significant relation between diabetes and hyperhomocysteinemia which is inconsistent with case control study was performed in Zhejiang University, which involved 150 patient with type 2 diabetes and control group which found that plasma Homocysteine level is significantly higher than the healthy group, p value < 0.001 and this is inconsistent with our result as the prevalence of hyperhomocysteinemia in diabetic patients 39.1% which render the p value 0.35 which is statistically insignificant.[56]

Also our result is consistent with case control study in University of Turku which investigated whether moderately elevated plasma homocysteine levels are independently related to increased incidence of fatal and nonfatal CHD events in persons with type 2 diabetes, this relation was also significant. [41]

We think this disagreement is because our sample size is much less than other studies, meanwhile the diabetic patients percentage 35.4% which account for 46 patients. There was no significant association between plasma homocysteine level and the incidence of acute coronary syndrome or with the subtypes. The same applied for the correlation with hypertension and diabetes which inconsistent with other researches.

In addition by using logistic regression test to explore the relative importance of predictors of hyperhomocysteinemia, we found none of the was a significant predictors.

The disagreement with other studies was because of relatively small sample size which was because of short duration of the study and limitation of financial funds (No fund was received for this study) as the homocysteine measurement kits are rather expensive.

## Limitation of the study:

A Small sample size, short duration of the study and absence of control group in the study. We depend on fasting serum Homocysteine level per se, and not use other diagnostic purposes as gene study and oral methionine load to detect borderline cases.

## Conclusion:

Hyperhomocysteinemia is prevalent in patients with acute coronary syndrome as (44.6%) of the patients had got high serum homocysteine level.

The level of homocysteine seems significantly related to smoking as (57.1%) of the smokers had hyperhomocysteinemia.

No significant variation in serum homocysteine level was found among different subtypes of ACS.

Hyperhomocysteinemia was not found to be significantly related to hypertension and diabetes.

## **Recommendation**:

We recommend:

1) To measure serum homocysteine level in patients with acute coronary syndrome.

2) To perform a larger study to evaluate the relationship with other risk factors and to study the hyperhomocysteinemia as an independent risk factor.

3) To perform a case control study to screen the patients with family history of premature cardiovascular diseases

4) To study the effect of homocysteine lowering on the overall CAD risk.

Table 1: Shows the frequency and percentage of age distribution among males and females.

| Sex | Age range/ years | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | 20-40 | | 41-60 | | 61-80 | | | |
| | No. | percentage | No. | Percentage | No. | percentage | No. | percentage |
| **Male** | 12 | 15.6% | 47 | 61% | 18 | 23.4% | 77 | 100% |
| **Female** | 2 | 3.8% | 43 | 81.1% | 8 | 15.1% | 53 | 100% |
| **Total** | 14 | 10.8% | 90 | 69.2% | 26 | 20% | 130 | 100% |

$X^2$ test= 6.97 df= 2 p value= 0.031

Table 2. Demonstrates the distribution of ACS categories among male and female patients.

| Sex | Acute Coronary Syndrome | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | STEMI | | NSTEMI | | UA | | | |
| | No. | percentage | No. | percentage | No. | Percentage | No. | percentage |
| **Male** | 51 | 66.2% | 23 | 29.9% | 3 | 3.9% | 77 | 100% |
| **Female** | 32 | 60.4% | 18 | 34% | 3 | 5.7% | 53 | 100% |
| **Total** | 83 | 63.8% | 41 | 31.5% | 6 | 4.6% | 130 | 100% |

$X^2$ test= 0.55 df= 2 p value= 0.76

Table 3 Demonstrates the distribution of ACS subtypes with different age range.

| ACS | Age range/ years | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | 20-40 | | 41-60 | | 61-80 | | | |
| | No. | Percent. | No. | Percent. | No. | Percent. | No. | Percent. |
| **STEMI** | 13 | 92.9% | 57 | 63.3% | 13 | 50% | 83 | 63.8% |
| **NSTEMI** | 1 | 7.1% | 27 | 30% | 13 | 50% | 41 | 31.5% |
| **UA** | 0 | 0% | 6 | 6.7% | 0 | 0% | 6 | 4.7% |
| **Total** | 14 | 100% | 90 | 100% | 26 | 100% | 130 | 100% |

$X^2$ test= 10.82 df= 4 p value= 0.029

Table 4: demonstrates the distribution of hyperhomocysteinemia among male and female patients:

| Sex | Homocysteine | | | | Total | |
|---|---|---|---|---|---|---|
| | >15 µmol/L | | <15 µmol/L | | | |
| | No. | percentage | No. | Percentage | No. | percentage |
| **Male** | 39 | 50.6% | 38 | 49.4% | 77 | 100% |
| **Female** | 19 | 35.8% | 34 | 64.2% | 53 | 100% |
| **Total** | 58 | 44.6% | 72 | 55.4% | 130 | 100% |

$X^2$ test= 2.78 df= 1 p value= 0.095

Table 5: demonstrates the prevalence of hyperhomocysteinemia according to the age.

| Age range/year | Homocysteine | | | | Total | |
|---|---|---|---|---|---|---|
| | >15 µmol/L | | <15 µmol/L | | | |
| | No. | percentage | No. | percentage | No. | percentage |
| **20-40** | 10 | 71.4% | 4 | 28.6% | 14 | 100% |
| **41-60** | 32 | 35.6% | 58 | 64.4% | 90 | 100% |
| **61-80** | 16 | 61.5% | 10 | 38.5% | 26 | 100% |
| **Total** | 58 | 44.6% | 72 | 55.4% | 130 | 100% |

$X^2$ test = 10.076 df= 2 p value= 0.006

Table 6: Demonstrate the prevalence of Hyperhomocysteinemia among ACS subtypes.

| ACS | Homocysteine | | | | Total | |
|---|---|---|---|---|---|---|
| | >15 µmol/L | | <15 µmol/L | | | |
| | No. | Percent. | No. | Percent. | No. | Percent. |
| **STEMI** | 38 | 45.8% | 45 | 54.2% | 83 | 100% |
| **NSTEMI** | 18 | 43.9% | 23 | 56.1% | 41 | 100% |
| **UA** | 2 | 33.3% | 4 | 66.7% | 6 | 100% |
| **Total** | 58 | 44.6% | 72 | 55.4% | 130 | 100% |

$X^2$ test= 0.36 df= 2 P value= 0.834

Table 7: Demonstrate the relationship between smoking and hyperhomocysteinemia.

| Smoking | Homocysteine | | | | Total | |
|---|---|---|---|---|---|---|
| | >15 µmol/L | | <15 µmol/L | | | |
| | No. | Percent. | No. | Percent. | No. | Percent. |
| **Smokers** | 44 | 57.1% | 33 | 42.9% | 77 | 100% |
| **Non smokers** | 14 | 26.4% | 39 | 73.6% | 53 | 100% |
| **Total** | 58 | 44.6% | 72 | 55.4% | 130 | 100% |

$X^2$ test= 11.99 df= 1 P value: 0.001

Table 8: Demonstrate the prevalence of Hyperhomocysteinemia in relation to hypertension.

| Homocysteine | hypertensive | | Non hypertensive | | Total | |
|---|---|---|---|---|---|---|
| | No. | Percent. | No. | Percent. | No. | Percent. |
| >15 µmol/L | 34 | 47.2% | 24 | 41.4% | 58 | 44.6% |
| <15 µmol/L | 38 | 52.8% | 34 | 58.6% | 72 | 55.4% |
| **Total** | 72 | 100% | 58 | 100% | 130 | 100% |

$X^2$ test= 0.44 df= 1 P value= 0.505

Table 9 demonstrates the relation between diabetes and Homocysteine level.

| Homocysteine | Diabetics | | Non diabetics | | Total | |
|---|---|---|---|---|---|---|
| | No. | Percent. | No. | Percent. | No. | Percent. |
| **>15 µmol/L** | 18 | 39.1% | 40 | 47.6% | 58 | 44.6% |
| **<15 µmol/L** | 28 | 60.9% | 44 | 52.4% | 72 | 55.4% |
| **Total** | 46 | 100% | 84 | 100% | 130 | 100% |

$X^2$ test= 0.87 df= 1 P value= 0.35

# REFERENCES:


1. McCully KS. Homocysteine and vascular disease. Nat Med 1996; 2:386.
2. Gaustadnes M, Rüdiger N, Rasmussen K, Ingerslev J. Intermediate and severe hyperhomocysteinemia with thrombosis: a study of genetic determinants. Thromb Haemost 2000; 83:554.
3. D'Angelo A, Coppola A, Madonna P. The role of vitamin B12 in fasting hyperhomocysteinemia and its interaction with the homozygous C677T mutation of the methylenetetrahydrofolate reductase (MTHFR) gene. A case-control study of patients with early-onset thrombotic events. Thromb Haemost 2000; 83:563.
4. Rosenson RS. Antiatherothrombotic effects of nicotinic acid. Atherosclerosis 2003; 171:87.
5. Dierkes J, Westphal S, Luley C. The effect of fibrates and other lipid-lowering drugs on plasma homocysteine levels. Expert Opin Drug Saf 2004; 3:101.
6. Bazzano LA, He J, Muntner P, et al. Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. Ann Intern Med 2003; 138:891.
7. Kang SS, Wong PW, Susmano A, et al. Thermolabile methylenetetrahydrofolate reductase: an inherited risk factor for coronary artery disease. Am J Hum Genet 1991; 48:536.
8. Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995; 10:111.

9. Gallagher PM, Meleady R, Shields DC, et al. Homocysteine and risk of premature coronary heart disease. Evidence for a common gene mutation. Circulation 1996; 94:2154.
10. Harmon DL, Woodside JV, Yarnell JW, et al. The common 'thermolabile' variant of methylene tetrahydrofolate reductase is a major determinant of mild hyperhomocysteinaemia. QJM 1996; 89:571.
11. Kluijtmans LA, Young IS, Boreham CA, et al. Genetic and nutritional factors contributing to hyperhomocysteinemia in young adults. Blood 2003; 101:2483.
12. Voutilainen S, Rissanen TH, Virtanen J, et al. Low dietary folate intake is associated with an excess incidence of acute coronary events: The Kuopio Ischemic Heart Disease Risk Factor Study. Circulation 2001; 103:2674.
13. Ubbink JB, Vermaak WJ, van der Merwe A, Becker PJ. Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia. Am J Clin Nutr 1993; 57:47.
14. Jacques PF, Selhub J, Bostom AG, et al. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. N Engl J Med 1999; 340:1449.
15. Rolland PH, Friggi A, Barlatier A, et al. Hyperhomocysteinemia-induced vascular damage in the minipig. Captopril-hydrochlorothiazide combination prevents elastic alterations. Circulation 1995; 91:1161.
16. Poddar R, Sivasubramanian N, DiBello PM, et al. Homocysteine induces expression and secretion of monocyte chemoattractant protein-1 and interleukin-8 in human aortic endothelial cells: implications for vascular disease. Circulation 2001; 103:2717.

17. Majors A, Ehrhart LA, Pezacka EH. Homocysteine as a risk factor for vascular disease. Enhanced collagen production and accumulation by smooth muscle cells. Arterioscler Thromb Vasc Biol 1997; 17:2074.
18. Al-Obaidi MK, Philippou H, Stubbs PJ, et al. Relationships between homocysteine, factor VIIa, and thrombin generation in acute coronary syndromes. Circulation 2000; 101:372.
19. Nappo F, De Rosa N, Marfella R, et al. Impairment of endothelial functions by acute hyperhomocysteinemia and reversal by antioxidant vitamins. JAMA 1999; 281:2113.
20. Mansoor MA, Bergmark C, Svardal AM, et al. Redox status and protein binding of plasma homocysteine and other aminothiols in patients with early-onset peripheral vascular disease. Homocysteine and peripheral vascular disease. Arterioscler Thromb Vasc Biol 1995; 15:232.
21. Stamler JS, Osborne JA, Jaraki O, et al. Adverse vascular effects of homocysteine are modulated by endothelium-derived relaxing factor and related oxides of nitrogen. J Clin Invest 1993; 91:308.
22. Stühlinger MC, Tsao PS, Her JH, et al. Homocysteine impairs the nitric oxide synthase pathway: role of asymmetric dimethylarginine. Circulation 2001; 104:2569.
23. Kanani PM, Sinkey CA, Browning RL, et al. Role of oxidant stress in endothelial dysfunction produced by experimental hyperhomocyst(e)inemia in humans. Circulation 1999; 100:1161.
24. Willems FF, Aengevaeren WR, Boers GH, et al. Coronary endothelial function in hyperhomocysteinemia: improvement after treatment with folic acid and cobalamin in patients with coronary artery disease. J Am Coll Cardiol 2002; 40:766.

25. van Guldener C, Stehouwer CD. Hyperhomocysteinaemia and vascular disease--a role for DNA hypomethylation? Lancet 2003; 361:1668.
26. Ingrosso D, Cimmino A, Perna AF, et al. Folate treatment and unbalanced methylation and changes of allelic expression induced by hyperhomocysteinaemia in patients with uraemia. Lancet 2003; 361:1693.
27. Kang SS, Wong PW. Genetic and nongenetic factors for moderate hyperhomocyst(e)inemia. Atherosclerosis 1996; 119:135.
28. Kang SS, Wong PW, Malinow MR. Hyperhomocyst(e)inemia as a risk factor for occlusive vascular disease. Annu Rev Nutr 1992; 12:279.
29. Dudman NP, Wilcken DE, Wang J, et al. Disordered methionine/homocysteine metabolism in premature vascular disease. Its occurrence, cofactor therapy, and enzymology. Arterioscler Thromb 1993; 13:1253.
30. Al-Obaidi MK, Stubbs PJ, Amersey R, Noble MI. Acute and convalescent changes in plasma homocysteine concentrations in acute coronary syndromes. Heart 2001; 85:380.
31. Christen WG, Ajani UA, Glynn RJ, Hennekens CH. Blood levels of homocysteine and increased risks of cardiovascular disease: causal or casual? Arch Intern Med 2000; 160:422.
32. Fallon UB, Ben-Shlomo Y, Elwood P, et al. Homocysteine and coronary heart disease in the Caerphilly cohort: a 10 year follow up. Heart 2001; 85:153.
33. Knekt P, Reunanen A, Alfthan G, et al. Hyperhomocystinemia: a risk factor or a consequence of coronary heart disease? Arch Intern Med 2001; 161:1589.

34. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002; 288:2015.
35. Klerk M, Verhoef P, Clarke R, et al. MTHFR 677C-->T polymorphism and risk of coronary heart disease: a meta-analysis. JAMA 2002; 288:2023.
36. Kohara K, Fujisawa M, Ando F, et al. MTHFR gene polymorphism as a risk factor for silent brain infarcts and white matter lesions in the Japanese general population: The NILS-LSA Study. Stroke 2003; 34:1130.
37. Humphrey LL, Fu R, Rogers K, et al. Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. Mayo Clin Proc 2008; 83:1203.
38. Giles WH, Croft JB, Greenlund KJ, et al. Association between total homocyst(e)ine and the likelihood for a history of acute myocardial infarction by race and ethnicity: Results from the Third National Health and Nutrition Examination Survey. Am Heart J 2000; 139:446.
39. Al-Obaidi MK, Stubbs PJ, Collinson P, et al. Elevated homocysteine levels are associated with increased ischemic myocardial injury in acute coronary syndromes. J Am Coll Cardiol 2000; 36:1217.
40. Matetzky S, Freimark D, Ben-Ami S, et al. Association of elevated homocysteine levels with a higher risk of recurrent coronary events and mortality in patients with acute myocardial infarction. Arch Intern Med 2003; 163:1933.

41. Soinio M, Marniemi J, Laakso M, et al. Elevated plasma homocysteine level is an independent predictor of coronary heart disease events in patients with type 2 diabetes mellitus. Ann Intern Med 2004; 140:94.
42. Genest JJ Jr, McNamara JR, Upson B, et al. Prevalence of familial hyperhomocyst(e)inemia in men with premature coronary artery disease. Arterioscler Thromb 1991; 11:1129.
43. Anderson JL, Muhlestein JB, Horne BD, et al. Plasma homocysteine predicts mortality independently of traditional risk factors and C-reactive protein in patients with angiographically defined coronary artery disease. Circulation 2000; 102:1227.
44. Hoogeveen EK, Kostense PJ, Jakobs C, et al. Hyperhomocysteinemia increases risk of death, especially in type 2 diabetes : 5-year follow-up of the Hoorn Study. Circulation 2000; 101:1506.
45. Schnyder G, Flammer Y, Roffi M, et al. Plasma homocysteine levels and late outcome after coronary angioplasty. J Am Coll Cardiol 2002; 40:1769.
46. Selhub J, Jacques PF, Bostom AG, et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. N Engl J Med 1995; 332:286.
47. Kelly PJ, Rosand J, Kistler JP, et al. Homocysteine, MTHFR 677C-->T polymorphism, and risk of ischemic stroke: results of a meta-analysis. Neurology 2002; 59:529.
48. Boysen G, Brander T, Christensen H, et al. Homocysteine and risk of recurrent stroke. Stroke 2003; 34:1258.
49. Kim NK, Choi BO, Jung WS, et al. Hyperhomocysteinemia as an independent risk factor for silent brain infarction. Neurology 2003; 61:1595.

50. Vasan RS, Beiser A, D'Agostino RB, et al. Plasma homocysteine and risk for congestive heart failure in adults without prior myocardial infarction. JAMA 2003; 289:1251.
51. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002; 325:1202.
52. Casas JP, Bautista LE, Smeeth L, et al. Homocysteine and stroke: evidence on a causal link from mendelian randomisation. Lancet 2005; 365:224.
53. Hankey GJ, Eikelboom JW. Homocysteine and stroke. Lancet 2005; 365:194.
54. Lewis SJ, Ebrahim S, Davey Smith G. Meta-analysis of MTHFR 677C->T polymorphism and coronary heart disease: does totality of evidence support causal role for homocysteine and preventive potential of folate? BMJ 2005; 331:1053.
55. Heux S,Morin F, Lea RA et al. the methylene tetrahydrofolate reductase gene variant (C677T) as a risk factor for essential hypertension in Caucasian , Japanese hypertensive research journal 2004 sep. 27(9):663-7.
56. Huang T, Asimi S et al, plasma phospholipid polyunsaturated fatty acids and homocysteine in Chinese type 2 diabetes patients. Asia Pacific journal of clinical nutrition 2012;21(3):394-9.
57. Kristian Thygesen, Joseph S. Alpert, Allan S. Jaffe, Maarten L. Simoons,Bernard R. Chaitman and Harvey D. White: theWriting Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial 2012.

# انتشار ارتفاع الهوموسستين للمرضى الذين يعانون من متلازمة قصور الشرايين التاجية الحادة

دراسة مقدمة إلى اللجنة العلمية المشرفة على دراسة الطب الباطني
كجزء من متطلبات نيل شهادة زمالة المجلس العراقي
للاختصاصات الطبية في الطب الباطني

من قبل

عمار صالح عبود

بكالوريوس طب وجراحة عامة

بإشراف الأستاذ

الدكتور عبد الرحيم حسن الحمراني

أُستاذ الطب الباطني

# الخلاصة

**المقدمة:** ارتفاع تركيزالهوموسستين في الدم هو عامل خطورة مستقل للأصابة بأمراض الاوعية الدموية الناتجة عن تصلب الشرايين و الجلطات الدموية الوريدية المتكررة.
الهوموسستين له خصائص تخثرية اولية تؤدي الى تصلب الشرايين.هنالك علاقة بين ارتفاع تركيز الهوموسستين بالدم و امراض القلب التاجية والذي يرتبط بزيادة الاصابة بامراض الاوعية الدموية التاجية و الدماغية.

**اهداف الدراسة:** تقديرمعدل انتشار ارتفاع تركيز الهوموسستين للمرضى الذين يعانون من متلازمة قصور الشرايين التاجية الحاد ومقارنة المستوى بين مختلف الانواع لقصور الشرايين التاجية مثل، احتشاء العضلة القلبية المرافق لارتفاع قطعة الاس تي وغير المرافق لارتفاع قطعة الاس تي و الذبحة الصدرية الغير مستقرة.
تحديد نسبة ارتفاع الهوموسستين للمرضى الذين يعانون من عوامل خطورة اخرى للاصابة بامراض القلب التاجية مثل التدخين،ارتفاع ضغط الدم وداء السكر.

**الطريقة:** 130 مريضا، 77 ذكور فئتهم العمرية(26-75 سنه) و بمتوسط عمري (52.20± 10.41) سنه و 53 اناث فئتهم العمرية (20-71 سنه) و بمتوسط عمري (53.47± 8.77) سنه ، تم تسجيلهم بالدراسة التي استمرت لمدة 16 شهرا في ردهة انعاش القلب في مستشفى البصرة العام. تم سحب عينة دم الصوم من المرضى و تم فحص الهوموسستين و نسبة الدهون ونسبة الكلوكوز بالدم و اليوريا و الكرياتنين، بالاضافة الى مستوى التروبونين . مستوى الهوموسستين الطبيعي للدراسة هو 15 ماكرومول|لتر.

**النتائج:** الدراسة اثبتت ان معدل انتشارارتفاع الهوموسستين هو 44.6% ( 39(50.6%) ذكور و 19(35.8%) اناث) لكن الفرق ليس ذو دلاله احصائية معتدة.بالاضافة ان احتشاء العضلة القلبية النترافق مع ارتفاع قطعة الاس تي اكثر انتشارا بالبالغين ضمن الفئة العمرية (20-40 سنة) ،احتشاء العضلة القلبية الغير مترافق مع ارتفاع قطعة الاس تي اكثر شيوعا

بالمرضى ذوي الفئة العمرية 60 سنه فما فوق بينما الذبحة الصدرية الغير مستقرة هي اكثر انتشارا لدى المرضى ذوي الفئة العمرية (41-60 سنة) و هذة العدلات ذو دلالة احصاءية معتدة.الدراسة اوضحت علاقة بين التدخين و ارتفاع مستوى الهوموسستين و هذا واضح بكون 44(57.1%) مريض مدخن لديهم ارتفاع مستوى الهوسستين بالدم و 33(42.9%) مدخن لديهم مستوى هوموسستين طبيعي، هذة العلاقة ذات دلالة احصائية معتدة.

**الاستنتاج:** الدراسة اثبتت ان ارتفاع مستوى الهوموسستين ذو انتشار في المصابين بمتلازمة قصور الشرايين التاجية الحادة بمختلف الفئات العمرية حيث 44.6% من المرضى لديهم مستوى هوموسستين مرتفع. ان ارتفاع الهوموسستين بالدم ذو علاقة احصائية معتدة مع التدخين حيث ان 57.1% من المدخنين لديهم مستوى مرتفع.

بالاضافة لذلك لايوجد اختلاف واضح احصائيا بمستوى الهوموسستين والاصابة بمختلف انواع متلازمة قصور الشرايين التاجية الحادة و هذا ينطبق على ارتفاع ضغط الدم و داء السكري.