

## The Effect of Nitrates and Sulphydryl Group in Treating Heart Disease (Angina Pectoris) on the Mortality Rate Reduction

Salah Abd-Al Kader Omran

Assist. Prof.

Cardiologist Al-Muthanna University,

college of Medicine, Iraq

Email: drsalahomran@yahoo.com



### Abstract

The research focused on nitrates and sulphydryl compounds with their various pharmacological types and their effect on heart disease (angina pectoris) because they pose a fatal danger and threaten people's lives, especially in the city of Samawah / Iraq, because the city was exposed to environmental pollution, fuels, wars, social life, poverty and the psychology of the individual, these factors On the increase in the death rate of patients, and sudden cardiac arrest and heart failure, the most prominent of which was angina pectoris. The research period was for a year 2022-2023. We randomly collected 950 patients of both sexes, especially after the age of 40 years, who start having heart symptoms in Samawah General Teaching Hospital and the Specialized Center for Diabetes. and endocrine, Through daily work using and developing nitrates and their effectiveness for patients of all kinds, and trying to avoid the barrier tolerance that loses the action of nitrates and the depletion of sulphydryl's from cells, we used to, (ACE Inhibitors , B-Blockers , Ca<sup>+2</sup> Channel blockers , Angiotensin II Receptor, Antihistamine ,diuretic , Anti serotine ,Aspirin (platelet inhibitor, Anticoagulants , Thrombolytic Agents ,Antidepressants, syrup Anti sputum NAC (N-Acetyl cysteine ) In addition to various drugs for the treatment of angina pectoris and drugs for chronic diseases that accompany the most deadly diseases in the development of heart diseases, in different and calculated doses, but all attempts were disappointing. The effect of depletion of the sulphydryl compound (SH grup) was depleted by the cells, Except in cases of seizure, intermittent exercise, and stress, effort , nitroglycerin is clear and beneficial. However, repeated and continuous exposure to high doses of organic nitrates leads to a noticeable attenuation in most of its side effects, such as a decrease in the ability of vascular smooth muscles to convert nitroglycerin into nitrogen oxide, or true vascular endurance, we used Multiple and multiplying mechanisms to benefit from nitrates for angina pectoris Diagnosis, treatment, and outcome, with the formula: Patient condition = therapeutic dose = heart attack = benefit from nitrates. It leads to the emergence of symptoms of angina, so the treatment was carried out as part of a comprehensive treatment program, And the most effective approach to nitrates to restore the response is to interrupt treatment 6-8 hours (rest period), which allows to restore efficacy. Most patients after the age of 40 years who suffer from heart diseases and chronic and accompanying (diagnostic-therapeutic program) found it 90% of patients when taking nitrates and patients Those who suffer from coronary arteries to dilate and widen and with narrowing of blood vessels, the benefit was  $\pm 85\%$  (the diameter of the vessel in the coronary artery was 200 micrometers, the response was high, while those of  $< 100$  respond to the minimum), and the myocardial oxygen demand decreased  $\pm 65\%$ , while the angina Unstable pectoralis ( Acute coronary syndrome (ACS) >>> (I.C.U) plays a major anti-platelet role (platelet inhibitors, Anticoagulants, Thrombolytic Agent ), so nitrates, beta-blockers, and calcium channel blockers are additionally effective. As for stenting (PCI) and cardiac surgery, a procedure to save the patient's life, the effect of nitrates was  $\pm 60\%$  , As for urgent myocardial infraction(MI) >>> (I.C.U) Although nitroglycerin is commonly given to relieve ischemic pain, all practical evidence indicates that nitrates improve mortality by 40%, a small percentage.

According to the American Association / American College of Cardiology (AHA / ACC)) nitrates should not be used in the case of low blood pressure because the direct cause of myocardial infarction is intracoronary thrombosis, so reperfusion treatments are very important and coronary interventions (PCI) uses stents, thrombolytic and platelets Patient life-saving  $\pm 80\%$  , As for the case of congestive heart failure, nitrates are not recommended and do not improve the death rate. Only isosorbide dinitrite (binary) can be given at night only. It can improve (orthopnea), reduce low voltage (effort) on the ventricles, reduce pulmonary congestion, and increase cardiac output in patients at a rate of  $\pm 2\%$  with extreme caution. As for Angina All stable types benefited from nitrates by  $80\% \pm$  , As an adjuvant within the treatment of angina pectoris. Those who did not respond to nitrates were replaced with calcium channel blocker , diltiazem, or carvedilol. It is not recommended to give nitrates and sudden withdrawal from them due to the emergence of side effects, instability of the patient, common headache, shortness of breath, and distance, Risk factors and control of chronic and accompanying diseases  $\pm 70\%$  It was very useful and effective for patients, The general rate of stability of cardiac conditions within the program  $\pm 75\%$  .

**Keyword:** Nitrate drug ECG , Cardiac Enzyme , Arrhythmia , cardiac catheter ( PCI ) , Laboratory Analyze , Halter , treadmill test, Echo study , Platelet Aggregation Inhibitors , Anticoagulants , Thrombolytic Drugs ,pacemaker , ( ICU ) .

## INTRODUCTION

**Nitrate NO<sub>3</sub>** It is a polyatomic ion, carrying a unit of negative charges and a molecular mass (62.0049 ) gram / mol. Our medical use of it is as a prevention of angina pectoris and myocardial infarction, as it reduces their occurrence. A **sulfhydryl group** (also called a "thiol group") consists of a sulfur atom with two lone pairs bonded to one hydrogen. The sulfhydryl group is ubiquitous in our bodies and is found mostly in oxidized form as disulfide bonds. Disulfide bonds contribute to the tertiary and quaternary structures of proteins. [5]

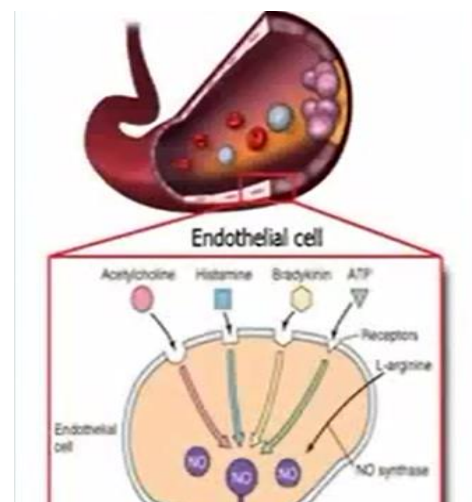
Organic nitrates (and nitrites) used in the treatment of angina pectoris are simple nitric and nitrous acid esters of glycerol. They differ in their volatility. For example, isosorbide dinitrate and isosorbide mononitrate are solids at room temperature, nitroglycerin is only moderately volatile, and amyl nitrite is extremely volatile. These compounds cause a rapid reduction in myocardial oxygen demand, followed by rapid relief of symptoms. They are effective in stable and unstable angina as well as in variant angina pectoris. [7,9]

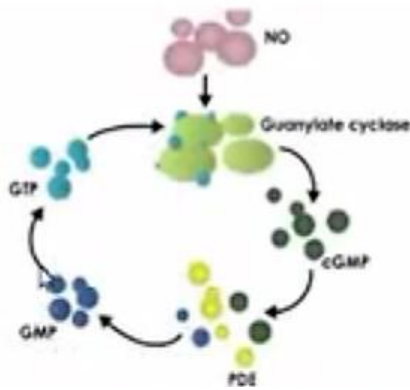
Organic Nitrate prototype of these agents is Nitroglycerin ( NG) or Glyceryl Trinitrate ( GIN) of its derivatives - Isosorbide dinitrate ( Isordil ) , - Isosorbide mononitrate ( Effax ) , - Nitroglycerin (Gall) , Nitroglycerin (transdermal patch ) , Nitroglycerin I.V ( In emergency cases and resuscitation ( ICU ) Angina , IM, cardiovascular disease Infusion solution 25mg / 250mL ( fluid ) or

50mg / 250 mL or 100 / 250 mL (fluid) , Spray (NG) , Sublingual (NG) . [1,3]

## Mechanism

Nitric oxide ( NO) is primarily produced by vascular endothelial cells > cause relaxation of vascular smooth muscle ( vasodilation ) , ( NO ) >> stimulate guanylate cyclase increase cyclic guanosine monophosphate (cGMP) >> Decrease Ca<sup>+2</sup> influx , Relaxation of vascular smooth muscle >> VD , ( NO ) also activates K<sup>+</sup> channels, which leads to hyperpolarization and relaxation. [4,6]



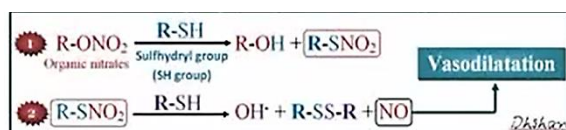


**Relive pain :**

Heart pain occurs with angina pectoris, chest pain, because the tissues of the body burn glucose in a process called glycolysis that occurs in the cytoplasm to obtain energy in the presence of oxygen in the blood. 8 ATP is released to obtain energy molecules,<sup>[10,11]</sup> but if coronary artery stenosis occurs and there is little or no oxygen, 2 ATP will come out. In order for the lactic acid to be released and accumulated, it is deposited in the cells and creates severe pain (core cycle). Therefore, the heart cells suffer from a lack of energy (food) and oxygen, especially during exertion, so that the pain appears angina pectoris. Imbalance between oxygen supply and oxygen demand .

**Sulfhydryl Group :**

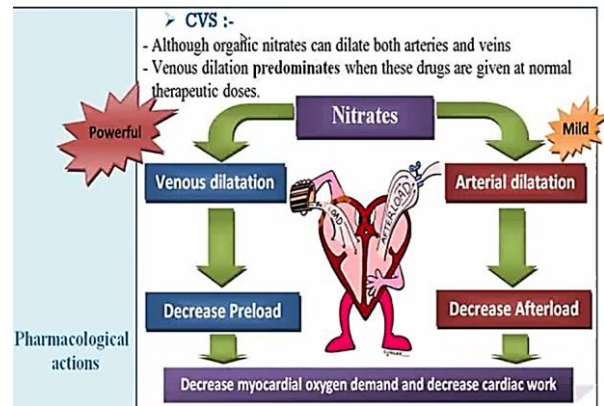
Organic nitrates are drugs that not directly release NO and not from NO within tissues , Nitrate group (NO<sub>2</sub>) IN organic nitrate interact with enzymes ( Nitric oxide synthase )and intracellular Sulfhydryl group ( R-SH ) ( SH group ) that reduce the nitrate group (NO<sub>2</sub>) TO Nitric Oxide ( NO ) .<sup>[12,13]</sup>



**Tolerance Nitrite**

When nitrates or their derivatives are used in frequent periods, there are intracellular substances called ( Sulfhydryl group ) depleted and reduced. Therefore, the state of tolerance occurs when the nitrate does not work, and the effect of this substance is lost. Therefore, when giving it, there must be a rest period (not giving) so that this substance may be formed again.<sup>[14,15]</sup>

Depletion of SH group > Cause nitrate tolerance .



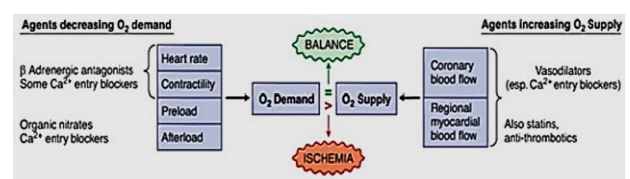
Therefore, nitrates are generally used in all types of (angina pectoris) that occur to humans (Stable Angina : classical , Typical , Exertional , Effort ) .Unstable Angina : Crescendo angina , preinfraction angina ) , ( Variant Angina : vasospastic , Prinzmetal s, inversa ) ,<sup>[16,17]</sup> The most important action of nitrates is Convert organic nitrate to nitric oxide And the( Sulfhydryl group ) that is consumed by continuing to take the drug without interruption without a break by stopping the drug for a certain period (Nitrate free interval period ) until the ( Sulfhydryl group ) compound is allowed to form again in the cells. <sup>[8,18]</sup>

**Avoid of tolerance**

- Giving a drug holiday ( Nitrate free interval period ) during the day ( 8-10) e.g. 7 am – 5 pm >> to allow regeneration of ( SH ) group .<sup>[19,20]</sup>
- Start the treatment with the smallest effective dose .
- Give SH containing compounds as NAC ( N-acetyl cysteine ) , Methioning ( which increase glutathione ( source of SH ) .
- Replacement of nitrates by another drugs e.g. Ca<sup>+2</sup> channel blockers and B- blockers .

**Side effects**

- Throbbing headache (cerebral vasodilation) .
- Postural hypotension .
- Reflux tachycardia .
- Drug rash ( allergy ) .
- Facial Flushing .<sup>[21]</sup>



## Objective

The extent of the effect of nitrates used in the treatment of various heart diseases, and work in two directions: reducing the tolerance of nitrates, and the second is treating heart diseases with nitrates, and reducing the death rate among people, and its effective role in saving the patient's life in the hospital and cardiopulmonary resuscitation, and the percentage of its effectiveness in the body.

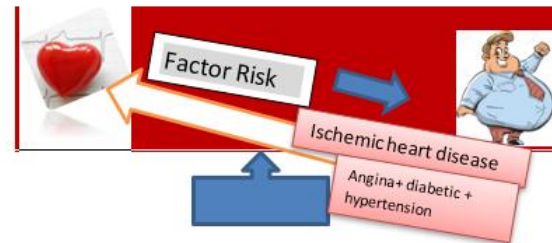
## METHOD AND MATERIAL

The clinical research component over the course of the year 2022-2023 by collecting a number of patients, 950 patients randomly, of both sexes, in the Samawah General Teaching Hospital and the Specialized Center for Diabetes and Endocrinology in Iraq, to receive daily patients who suffer from heart diseases, especially (angina pectoris), who are reviewers in consultations and admission to the hospital And resuscitation and patient files to assess the pathological conditions, the target response and the effect of nitrates (nitroglycerine, Isosorbide dinitrate and Isosorbide mononitrate in different forms spray, bag, under the tongue in addition to emergency cases with a nutrient solution intravenously at a calculated dose and time and monitored by the pressure and pulse and the patient's condition is calculated). In addition to medicines for angina pectoris and the most deadly associated chronic diseases and development of heart diseases, the work was to reduce tolerance for nitrates in the treatment of heart diseases (nitrate tolerance) and the extent of their benefit. Various drugs were used in our experience, namely (ACE Inhibitors , B-Blockers , Ca<sup>2+</sup> Channel blockers , Angiotensin II Receptor, Antihistamine ,diuretic , Anti serotine ,Aspirin (platelet inhibitor, Anticoagulants , Thrombolytic Agents ,Antidepressants, syrup Anti sputum NAC (N-Acetyl cysteine ), Through work, these drugs were given for calculated periods and in specific quantities, but all attempts were disappointing. The effect was that the sulfhydryl compound (SH) was depleted from the body, and the patient did not benefit fully, except in cases of seizures, intermittent exercise, and stress. Nitroglycerin is clear and beneficial. However, the Repeated or continuous exposure to high doses of organic nitrates results in a marked attenuation in the magnitude of most of their pharmacological effects. Tolerance may result from decreased ability of vascular smooth muscle to convert nitroglycerin to NO, true vascular tolerance, or activation of tolerance. Volume of tolerance is a

function of dose and frequency of use. We used multiple and multiple mechanisms to benefit from nitrates for angina pectoris and to prolong the life of the patient.. Because as a result of exacerbation of high blood pressure, anemia, thyrotoxicosis, obesity, heart failure, arrhythmia, and acute anxiety, it led to the emergence of angina symptoms in many cases, especially diabetes, so it is Treatment as part of a comprehensive treatment program. The most effective approach to nitrates to restore response is to interrupt treatment for 8-10 hours each day (Holiday), allowing efficacy to be restored. Most of the patients were over 40 years of age who suffer from heart diseases, chronic diseases, and comorbidities, and they were admitted to a [diagnostic-therapeutic] program and follow-up; 90% of patients with nitrates from patients with coronary artery dilation and vasoconstriction benefited  $\pm$  85% (vessel diameter is an important determinant of response to nitroglycerin. Vessels larger than 200  $\mu$ m in diameter are highly responsive, while those >100 Micrometers respond to the minimum level, and the myocardial demand for oxygen decreases by  $\pm$  65%. As for unstable myocardial infarction, it plays a major role in antiplatelet (anti-aggregate, anti-coagulant, anti-thrombus) so Nitrates and beta-blockers, calcium channel Inhibiter become extra (additional) effective.. As for the stent (PCI) and cardiac surgery, a procedure to save the patient's life, so the effect of nitrates was  $\pm$ 60% and the increase in the oxygen volume of the heart muscle, As for (urgent) Acute Myocardial Infarction-ST elevation, despite what is common among us, nitroglycerine is given to relieve ischemic pain, but all clinical evidence indicates that nitrates slightly improve the mortality rate by  $\pm$ 40%, according to the association's guidelines. American / American College of Cardiology (AHA / ACC) Nitrates should not be used in the case of hypotension, because the direct cause of myocardial infarction is intracoronary blood clots. Reperfusion therapies are very important and coronary interventions (PCIs) uses stents, thrombolytic drugs and rescue platelets The life expectancy of the patient is  $\pm$  80%. As for the case of congestive heart failure, it is not recommended to give nitrates, and the death rate does not improve. It is only possible to give Isosorbide dinitrate (dual) at night. It can improve orthopnea and reduce the low voltage on the ventricle, and in relieving pulmonary congestion and increasing cardiac output, it was given to patients 2% of them with extreme caution. As for stable angina of all kinds, 80% of nitrates

benefited. As an adjunct within the treatment, as for the patients who showed no response to nitrates and the emergence of side effects and were replaced (calcium channel Inhibiter , diltiazem, carvedilol, consumed a PDE5 inhibitor with great caution and for a short time) and the added drugs (anti-aggregation , statins, the percentage of patients was ± 7%, It is not recommended to give nitrates and the sudden withdrawal of nitrates due to the appearance of side effects, instability of the patient, common headache and shortness of breath, especially in chronic cases. Removal and treatment of the risk factors surrounding the patient such as pollution, stress, increased fat, kidney function, cumulative sugar, heart disease, and associated diseases were involved in a way. Positive improvement with a decrease in the death rate and a prolongation of the patient's life by ± 70%, and clinical trials and work

have proven through early periodic laboratory analyzes, food care, weight loss, exercise, medication, and the organization of the patient's life, a significant progress until the post-treatment stage to health resorts to rehabilitate patients to their health status Natural, as in the table showing the types of nitrates used according to the lead line and the British and American references:



**Table No. (1) Types of nitroglycerin used in treatment( I.H.D ) :**

	Preparation ( drug )	Peak action	Duration of action
1.	Sublingual GTN or spry	4-8 mins	10-30 mins
2.	Buccal GTN	4-10 mins	30-300 mins
3.	Transdermal GTN	1-3 hrs	Up to 24 hrs
4.	Oral isosorbide dinitrate	45-120 mins	2-6 hrs
5.	Oral isosorbide mononitrate	45-120 mins	6-10 hrs

**Table No. (2) Professional classification of angina pectoris and effective drugs for its treatment :**

N <sup>o</sup>	Angina pectoris	Nitrate	B-Block	Calcium channel	Anti-Aggregate	Statin
1.	Stable Angina : other name	+++	++	++	+++	+++
	Classical Angina	+++	++	++	+++	+++
	Typical Angina	+++	++	++	+++	+++
	Exertional Angina	+++	++	++	+++	+++
	Effort Angina	+++	++	++	+++	+++
2.	Unstable Angina	+++	++	++	+++Anti-Anticoagulant + PCIs	+++
	-Crescendo Angina	+++	++	++		+++
	-Preinfarction Angina	+++	++	++		+++
3.	Variant Angina	+++	--	++	++	++
	Vasospastic Angina	+++	--	++	++	++
	Prinzmetal s Angina	+++	--	++	++	++
	Angina inversa	+++	--	++	++	++
4.	Acute Myocardial Infarction-ST elevation	+++	++	++	++ Thrombolytic Drugs + PCIs	+++

**RESULTS**

The scientific and clinical results of nitrates were in two directions: the first is to reduce the translocation of nitrates. The work is done by using a group of different drugs that work to overcome this barrier in heart disease (stable and unstable angina as well as in

variant angina pectoris) On patients of both sexes, but it was disappointing. The effect was the permeation of the sulfhydryl compound (SH) from the body and the patient did not benefit fully, except in cases of seizures, intermittent exercise and stress. Nitroglycerin is clear and beneficial. However,

repeated or continuous exposure to high doses of Organic nitrates lead to a significant attenuation in the magnitude of most of its pharmacological effects. Tolerance may result from a decrease in the ability of vascular smooth muscles to convert nitroglycerin into nitrogen oxide. We used multiple and multiple mechanisms to benefit from nitrates for angina pectoris and prolong the patient's life. The patients were admitted to a comprehensive program (diagnostic-therapeutic), and the exclusion of the influencing risk factors, chronic diseases, and comorbidities. Patients when taking nitrates from patients who suffer from coronary arteries to dilate and prevent narrowing of blood vessels benefit  $\pm 85\%$ , and the myocardial demand for oxygen decreases,  $65\% \pm$  , As for unstable myocardial infarction, it plays a major role in platelet antibody (anti-aggregate, anti-coagulant, anti-thrombus (plaque rupture) so nitrates and beta-blockers, calcium channel Inhibiter , extra become additionally effective.. As for stenting (PCI) and cardiac surgery, a salvage procedure Therefore, the effect of nitrates was  $\pm 60\%$ , while (URGENT) Acute Myocardial Infarction-ST elevation) , despite the common among use, nitroglycerin is given to relieve ischemic pain, but all clinical evidence indicates that nitrates slightly improve the mortality rate  $\pm 40\%$ , and for myocardial infarction, it is intracoronary blood clotting, so reperfusion treatments are very important and interventions Coronary (PCIS) stent use, thrombolytic, and platelets save patient life  $\pm 80\%$  , As for the case of congestive heart failure, nitrates are not recommended and do not improve mortality. Only Isosorbide dinitrite (dual) can be given at night. It can improve orthopnea, reduce low voltage on the ventricles, reduce pulmonary congestion and increase cardiac output. It was given to patients  $\pm 2\%$  of them with extreme caution. As for stable myocardial infarction of all types, nitrates benefited by  $\pm 80\%$  as an adjuvant within the treatment. As for the patients who showed no response to nitrates and the emergence of side effects, and they were replaced (calcium channel Inhibiter , diltiazem, carvedilol, consumed a PDE5 inhibitor with great caution for a short time) and the added drugs (anti-aggregate , statins, the percentage of patients was  $\pm 7\%$ . It is not recommended to give nitrates and withdraw The sudden appearance of nitrates due to the emergence of side effects, instability of the patient, common headaches and shortness of breath, especially in chronic cases, removing and treating the risk factors surrounding

the patient such as pollution, stress, increased fat, kidney function, cumulative sugar, heart disease, and associated diseases contributed positively to an improvement in a decrease in the death rate And extending the life of the patient by  $\pm 70\%$ , the general rate of stability of cardiac conditions within the program is  $\pm 75\%$ .

### Tactics

The method of work was based on scientific sources and adherence to the system of work and in the prescribed doses of medicine in the treatment of heart diseases And at intermittent periods to ensure its work, according to the diagnosis, pathological analyzes, and other cardiac catheterization interventions that were approved for the safety of the patient's life, receiving medicine, and complete health care

### Technique

We relied on the art and skill of the work and the medical experience of the practitioners in the medical work.. The effect of doses and administration of Thrombolytic (Acetylate and Streptokinase) in resuscitation and nitrates with high accuracy and continuous monitoring on the monitor to monitor the heart and the changes that occur in (ECG) and the DC shock device was The rapid work of the cases (AF, VF, Cardiac Arrest, MI), and the critical cases in which the patient is between life and death were all side effects of angina pectoris, all of which gave us the necessary idea about the action of nitrates, and accompanying medicines for the treatment of angina .

### Discussion

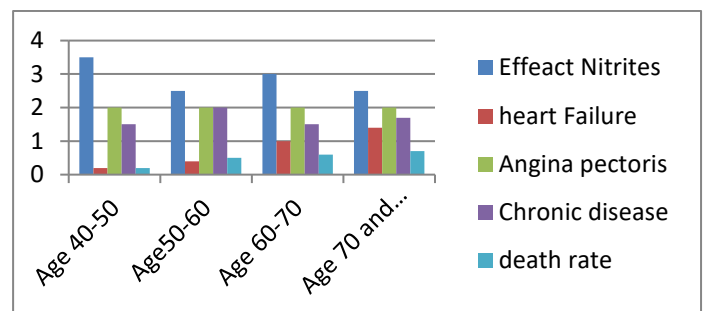
The choice to search for nitrates in the treatment of angina pectoris is of great importance in the research and development of this drug for us for what the patient is exposed to, especially in Iraq, an area that has been exposed to pollution, fuel, wars and nervous shocks, which negatively affected people in the spread of fatal heart diseases that caused deaths and an increase in the death rate .. Therefore, we adopted the scientific and clinical foundations in the work, dividing the patients into groups, and giving nitrates within the angina medications, and we noticed its effect on the types of angina pectoris. We used a group of drugs to bypass the threshold, but it was disappointing. . But the sulfhydryl compound makes the nitrate less effective than repeated use, so the solution was a 6-8 hour period by not giving the medicine in the majority of patients successfully, and

we used it for all types of angina pectoris and related diseases and congestive heart failure (a small percentage only at night) And what the patient suffers from are fatal symptoms, and it has been proven to us in the wide range of the use of nitrates and the obstacles and reasons that hinder its work in treatment and prevention and reduce the death rate if used in time and the correct and appropriate diagnosis, especially in heart attacks, and in the contraction or narrowing of the coronary artery according to the place and situation and the use of the alternative in the case Do not give for its side effects, that heart disease occurs to exacerbate chronic diseases High blood pressure, cholesterol, obesity, hereditary factor, nature of work and life habits, stress, are all risk factors, all of which have been removed in a comprehensive program with a periodic schedule that reviews the patient and receives treatment and guidance. Food and exercise had the greatest effect in reducing the death rate and cardiac injuries and prolonging the life of the patient within a scientific plan. Catheterization, stent and surgical interventions were life-saving for the patient.

## CONCLUSION

The best motive for the research is the prevalence of heart disease, angina pectoris, in the city of Samawah / Iraq, and its exacerbation for many reasons, especially after the age of 40 years, and the increase in the death rate for reasons related to the environment, habits, wars, pollution, and chronic and accompanying diseases. The motive for the research was to stop the deterioration of cases and the sudden death of patients. And we expanded it and as a window to prolong the life of the patient, we tried using a group of drugs to reduce the symptoms, for a period of one year, 950 patients of both sexes and in groups, and the results were disappointing , We followed another mechanism and linked nitrates to a period of time by not giving 6-8 hours, removed the risk factors, and introduced patients to a comprehensive, periodic treatment program for follow-up and treatment. Contraindications and contraindications according to work capacity, effect, and impact on patients. We monitored our efforts to modify the patient's social and psychological life.. and to control chronic diseases, the most deadly of which is diabetes mellitus, And early diagnosis, treatment, pathological analyzes, and diagnostic physiological tests that limit and early prevention and measures to suppress the exacerbation of various pathological conditions.. and remove the specter of

death and heart attacks with medication, catheterization, surgical interventions, and early prevention. Therefore, the death rate was reduced by 70% and the patient's life was extended by 80% from the response of patients who received Suffering from heart and chronic diseases and accompanying and directing the government to have specialized centers concerned with patients and rehabilitating patients after recovery in special resorts that have hospitals for the rehabilitation of patients (santorium) and their enjoyment of health and benefit from the medical services provided to him.



**Graph the effect of nitrates on heart disease in the (comprehensive therapeutic program)**

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