THYROID DYSFUNCTION AS CO-MORBID CONDITION IN CARDIOVASCULAR EVENTS IN ELDERLY PATIENT

Submitted By

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Dissertation submitted to

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Under the guidance of

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2011

DECLARATION BY THE CANDIDATE

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LIST OF ABBREVIATIONS

CVD – Cardiovascular Disease

T4 – Thyroxine

T3 – Triiodothyronine

TTF - Thyroid transcription factor

Tg – Thyroglobulin

TPO – Thyroid peroxidase

TSH – Thyroid stimulating hormone

THS-R – Thyroid stimulating hormone receptor

NIS – Na^+/I^- sympoter

MIT – Monoiodotyrosine

DIT – Diiodotyrosine

GPCR – G protein coupled receptor

TSI – Thyroid stimulating immunoglobulins

TTR – Transthyretin / Thyroxine binding prealbumin(TBPA)

TBG – Thyroid binding globulin

µg – microgram

TRs – Thyroid hormone receptor (α and β)

TSH – Thyroid stimulating hormone

Ab – Antibody

FT3 – Free Triiodothyronine

FT4 – Free Thyroxine

TT3 – Total Triiodothyronine

TT4 – Total Thyroxine

pg- picogarm

ng- nanogram

SVR – Systemic vascular resistance

RAAS – Renin-angiotensin-aldosterone system

DAP – Diastolic atrial pressure

SAP – Systolic atrial pressure

LV – Left ventricle

LVEDV – Left ventricle end diastolic volume

LVESV – Left ventricle end systolic volume

MAP – Mean arterial pressure

WHO – World Health Organization

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

Out of an estimated 58 million deaths globally from all causes in 2005, cardiovascular disease (CVD) accounted for nearly 30 %. Out of which a substantial proportion of these deaths (46%) were of people under 70 years of age due to cardiovascular disease.[1]

Improvements in medical diagnostic and therapeutics along with improved social conditions during the last few decades have increased the life span of man. According to 2001 census, 7.7% of total population of India was above the age of 60 years, which gives us a larger population base with special needs, and it continues to grow.[2]

In medical practice and hospital setup 20-25% of all medical admission are due to cardiovascular disease, so there is a greater need to understand this disease and prevent it from happening.[3]

Although established risk factors explain most cardiac events, significant attention is now being focused on alternative biochemical markers to assist in identifying those at increased risk of a clinical cardiac event.

Some studies have suggested that abnormal levels of thyroid stimulating hormone (TSH) may represent a novel cardiac risk factor. [4a b c]

OBJECTIVE

To study Thyroid dysfunction as co-morbid condition in Cardiovascular events in Elderly patient

REVIEW OF LITERATURE

THE THYROID GLAND

The thyroid gland produces two related hormones, thyroxine (T_4) and triiodothyronine (T_3) acting through nuclear receptors, these hormones play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult.

Disorders of the thyroid gland can either stimulate the overproduction of thyroid hormones (*thyrotoxicosis*) or cause glandular destruction and hormone deficiency (*hypothyroidism*).

Anatomy and Development

The thyroid (Greek *thyreos*, shield, plus *eidos*, form) consists of two lobes that are connected by an isthmus. It is located anterior to the trachea between the cricoid cartilage and the suprasternal notch. The normal thyroid is 12–20 g in size, highly vascular, and soft in consistency. Four parathyroid glands, which produce parathyroid hormone, are located posterior to each pole of the thyroid.

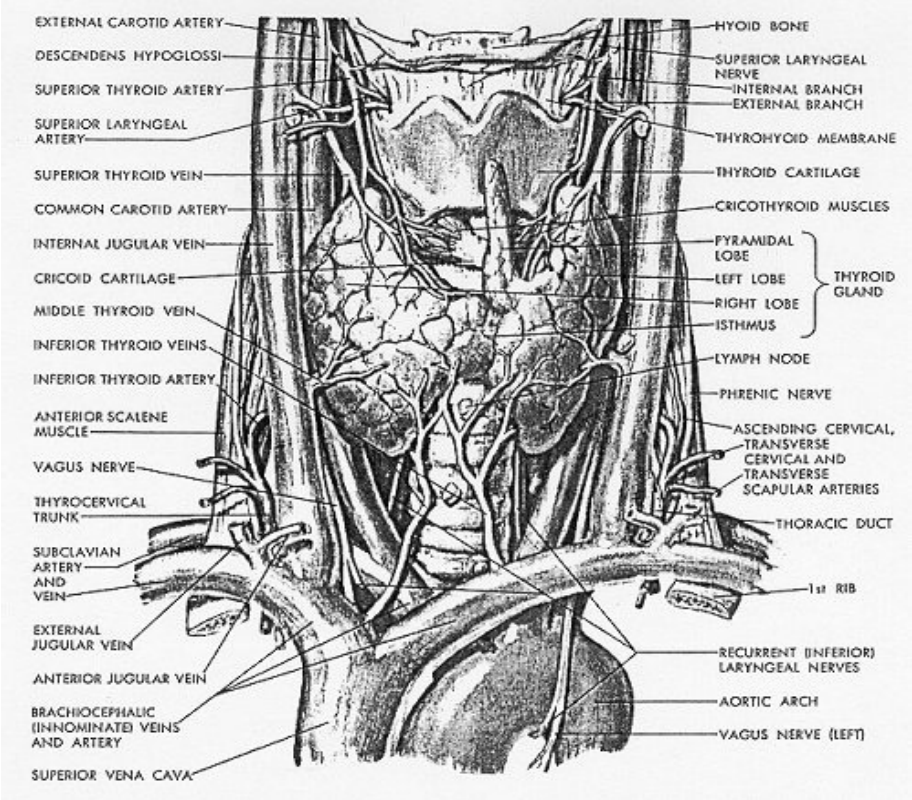
The recurrent laryngeal nerves traverse the lateral borders of the thyroid gland and must be identified during thyroid surgery to avoid vocal cord paralysis. The hyroid gland develops from the floor of the primitive pharynx during the third week of gestation. The developing gland migrates along the thyroglossal duct to reach its final location in the neck.

Neural crest derivatives from the ultimobranchial body give rise to thyroid medullary C cells that produce calcitonin, a calcium-lowering hormone. The C cells are interspersed throughout the thyroid gland, although their density is greatest in the

juncture of the upper one-third and lower two-thirds of the gland. Thyroid gland development is orchestrated by the coordinated expression of several developmental transcription factors.

Thyroid transcription factor (TTF) 1, TTF-2, and paired homeobox-8 (PAX-8) are expressed selectively, but not exclusively, in the thyroid gland. In combination, they dictate thyroid cell development and the induction of thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (NIS), and the thyroid-stimulating hormone receptor (TSH-R).

Mutations in these developmental transcription factors or their downstream target genes are rare causes of thyroid agenesis or dyshormonogenesis, though the causes of most forms of congenital hypothyroidism remain unknown.

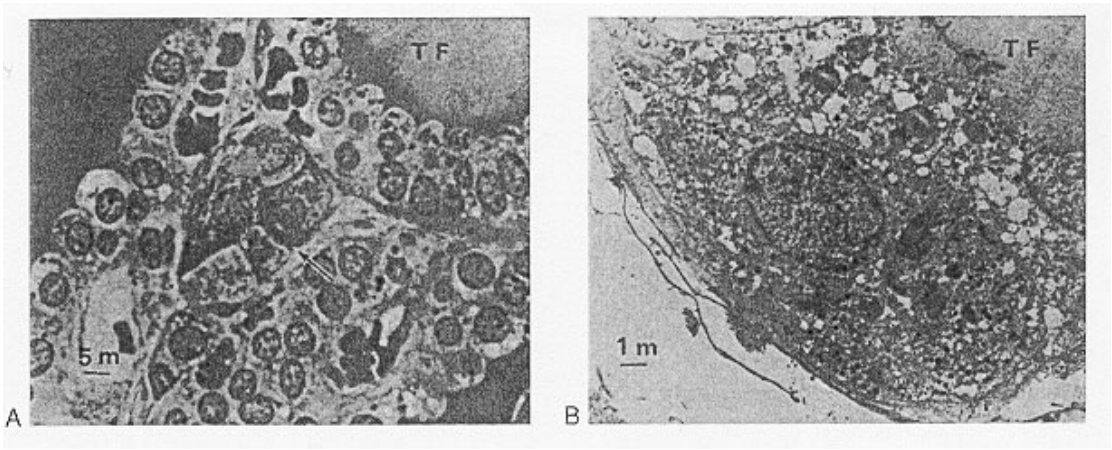


Netter FH, The Ciba Collection of Medical Illustrations, vol. 4, Endocrine system and selected metabolic diseases, Ciba, 1965

The Secretory Unit - The Follicle

Thyroid is composed of follicles or acini (the primary, or secretory, units of the organ). The cells of the follicles are the makers of hormone; the lumina are the storage depots. The walls consist of a continuous epithelium one cell deep, the parenchyma of the thyroid (the height of the epithelium is often inversely proportional to the diameter of the lumen of the follicle.) In addition to the acinar cells, there are individual cells or small groups of cells, C-cells, secrete calcitonin (or "thyrocalcitonin"). The thyroid follicular cells are polarized—the basolateral surface is apposed to the bloodstream and apical surface faces the follicular lumen.

Increased demand for thyroid hormone is regulated by thyroid-stimulating hormone (TSH), which binds to its receptor on the basolateral surface of the follicular cells, leading to Tg reabsorption from the follicular lumen and proteolysis within the cell to yield thyroid hormones for secretion into the bloodstream.



(A) Light microscopy of a parafollicular cluster (arrow) in relationship to thyroid follicle (TF) (x900). (B) Parafollicular cell in characteristic position between follicular cells and follicular basement membrane, not abutting on colloid (TF) (x4,200 (From Teitelbaum et al. Nature, 230,1971)

CONTROL OF THYROID FUNCTION

Thyroid Hormone Synthesis

Thyroid hormone synthesis requires the uptake of iodide by active transport, thyroglobulin biosynthesis, oxidation and binding of iodide to thyroglobulin, and within the matrix of this protein, oxidative coupling of two iodotyrosines into iodothyronines.

Iodide Transport

Iodide is actively transported by the iodide Na^+/I^- symporter (NIS) against an electrical gradient at the basal membrane of the thyrocyte and diffuses, following the electrical gradient, by a specialized channel (pendrin or another channel) from the cell to the lumen at the apical membrane.

After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide.

Iodide Binding to Protein and Iodotyrosine Coupling

Iodide oxidation and binding to thyroglobulin and iodotyrosine coupling in iodothyronines are catalyzed by the same enzyme, thyroperoxidase, with H_2O_2 used as a substrate. The reactive iodine atom is added to selected tyrosyl residues within Tg, a large (660 kDa) dimeric protein that consists of 2769 amino acids.

The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T_4 or T_3 can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines.

After coupling, Tg is taken back into the thyroid cell, where it is processed in lysosomes to release T_4 and T_3.

Uncoupled mono- and diiodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones.

Thyroid Hormone Secretion

Secretion of thyroid hormone requires endocytosis of human thyroglobulin, its hydrolysis, and the release of thyroid hormones from the cell. Thyroglobulin can be ingested by the thyrocyte by three mechanisms

a) Macropinocytosis

b) Micropinocytosis

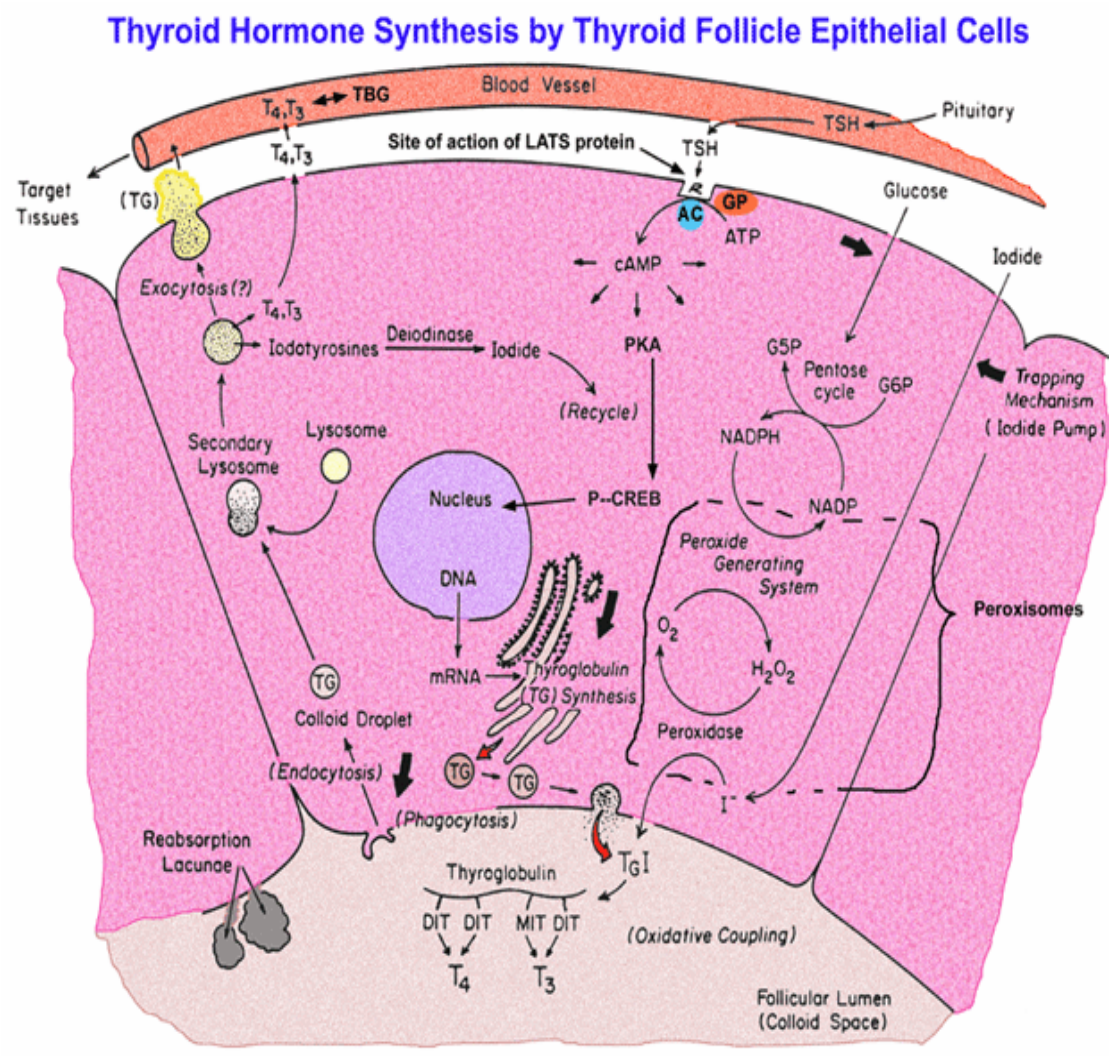
c) Receptor-Mediated Endocytosis(hypothesized)

The free thyroid hormones are released by an unknown mechanism, which may be diffusion or transport. The thyroid also releases thyroglobulin.

Functional Heterogeneity

It has long been known that at any given time the function of the thyroid follicles is not homogeneous. For instance, after injection of radioiodide, some follicles will incorporate important amounts of radioiodine while others will not incorporate at all. Similarly, after stimulation with TSH in in vivo thyroids or in in vitro incubated slices, some cells will develop pseudopods for macropinocytosis whithin 15 min while others submitted to the same stimulus will only respond after one to two hours.

In a beautiful study, Gérard et al showed in human thyroids that while some follicles exhibit marked expression of pendrin, TPO and THOX, others did not. The expressing follicles were that containing iodinated thyroglobulin. They correspond to larger capillary networks and to the expression in the follicular cells of vascular regulators nitric oxide synthase and endothelin. This shows the existence of active and inactive angiofollicular units. It suggests that over time angiofollicular units cycle from active to inactive states and that this is controlled by the follicular cells. It would be interesting to know if the inactive state corresponds to a lower sensitivity to TSH.



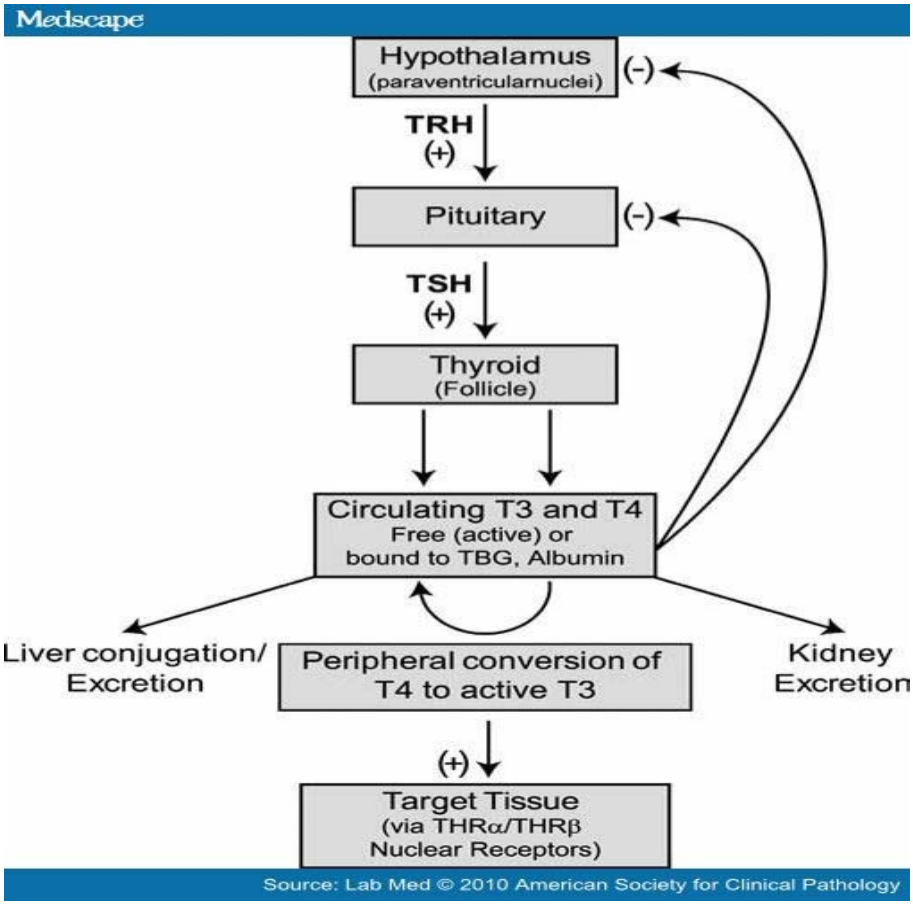
(Modified from Hadley, *Endocrinology, 4th Ed,* Prentice Hall: Upper Saddle River, NJ, 1996.)

CONTROL OF HORMONE SYNTHESIS

The most important controlling factors are iodine availability and TSH Inadequate amounts of iodine lead to inadequate thyroid hormone production, increased TSH secretion and thyroid stimulation, and goiter in an attempt to compensate

THS effects on secretion appear to be mediated through the cAMP cascade, while the effects on synthesis are mediated by the Gq/phospholipase C cascade.

TSH stimulates the expression of NIS, TPO, Tg and the generation of H_2O_2, increases formation of T3 relative to T4, alters the priority of iodination and hormonogenesis among tyrosyls and promotes the rapid internalization of Tg by thyrocytes.



REGULATION OF THE THYROID AXIS

TSH, secreted by the thyrotrope cells of the anterior pituitary, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action.

TSH is a 31-kDa hormone composed of α and β subunits; the α subunit is common to the other glycoprotein hormones [luteinizing hormone, follicle-stimulating hormone, human chorionic gonadotropin (hCG)], whereas the TSH β subunit is unique to TSH.

The extent and nature of carbohydrate modification are modulated by thyrotropin-releasing hormone (TRH) stimulation and influence the biologic activity of the hormone. The thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic TRH stimulates pituitary production of TSH, which, in turn, stimulates thyroid hormone synthesis and secretion.

Thyroid hormones feed back to inhibit TRH and TSH production The "set-point" in this axis is established by TSH. TRH is the major positive regulator of TSH synthesis and secretion. Peak TSH secretion occurs ~15 min after administration of exogenous TRH. Reduced levels of thyroid hormone increase basal TSH production and enhance TRH-mediated stimulation of TSH.

High thyroid hormone levels rapidly and directly suppress TSH gene expression secretion and inhibit TRH stimulation of TSH, indicating that thyroid hormones are the dominant regulator of TSH production. Like other pituitary hormones, TSH is released in a pulsatile manner and exhibits a diurnal rhythm; its highest levels occur at night. However, these TSH excursions are modest in comparison to those of other pituitary hormones, in part because TSH has a relatively

long plasma half-life (50 min). Consequently, single measurements of TSH are adequate for assessing its circulating level. TSH is measured using immunoradiometric assays that are highly sensitive and specific.

These assays readily distinguish between normal and suppressed TSH values; thus, TSH can be used for the diagnosis of hyperthyroidism (low TSH) as well as hypothyroidism (high TSH).

Short and ultra short-loop feedback control of TSH secretion

Evidence is accumulating that pituitary TSH is able to inhibit TRH secretion at hypothalamic level (short feedback) and TSH secretion at pituitary level (ultra short feedback). The precise physiological role of short and ultra-short feedback in controlling TRH/TSH secretion remains to be elucidated. It may be speculated that they concur in the fine tuning of the homeostatic control and in the generation of the pulsatility of TSH secretion.

TSH ACTION

TSH regulates thyroid gland function through the TSH-R, a seven-transmembrane G protein–coupled receptor (GPCR). The TSH-R is coupled to the α subunit of stimulatory G protein (G_s α), which activates adenylyl cyclase, leading to increased production of cyclic AMP.

TSH also stimulates phosphatidylinositol turnover by activating phospholipase C. The functional role of the TSH-R is exemplified by the consequences of naturally occurring mutations. Recessive loss-of-function mutations cause thyroid hypoplasia and congenital hypothyroidism.

Dominant gain-of-function mutations cause sporadic or familial hyperthyroidism that is characterized by goiter, thyroid cell hyperplasia, and autonomous function. Most of these activating mutations occur in the transmembrane domain of the receptor. They are thought to mimic the conformational changes induced by TSH binding or the interactions of thyroid-stimulating immunoglobulins (TSI) in Graves' disease.

Activating TSH-R mutations also occur as somatic events and lead to clonal selection and expansion of the affected thyroid follicular cell Other Factors that Influence Hormone Synthesis and Release

STIMULATORY

- Thyrotropin-releasing hormone (TRH)
- Prostaglandins (?)
- α-adrenergic agonists (? Via TRH)
- Opioids (humans)

- Arginin-vasopressin (AVP)
- Glucagon-like peptide 1 (GLP-1)
- Galanin
- Leptin
- Glucocorticoids (in vitro)

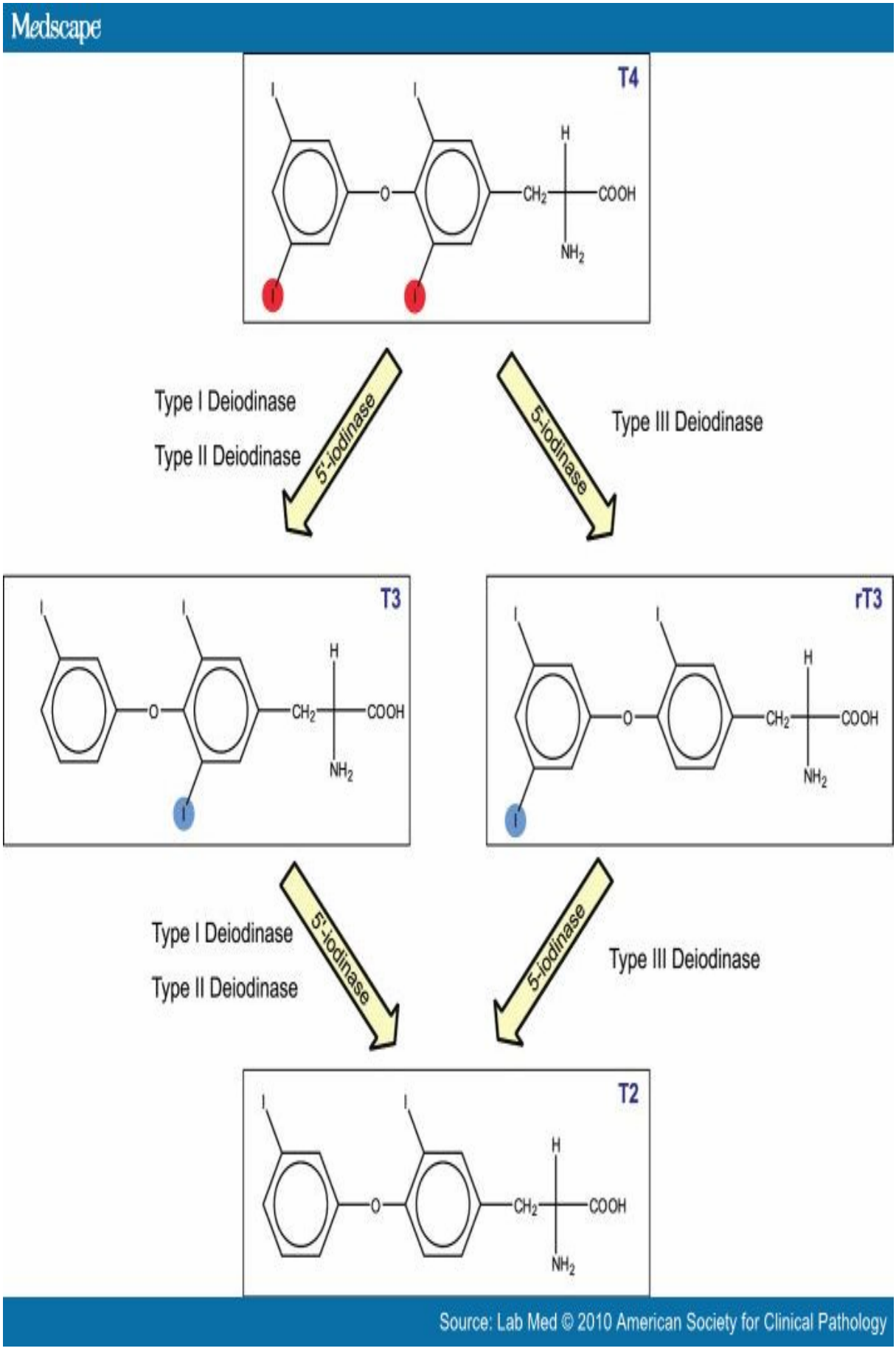
INHIBITORY

- Thyroid hormones and analogues
- Dopamine
- Gastrin
- Opioids (rat)
- Glucocorticoids (in vivo)
- Serotonin
- Cholecystokinin (CCK)
- Gastrin-releasing peptide (GRP)
- Vasopressin (AVP)
- Neuropeptide Y (NPY)
- Interleukin 1β and 6
- Tumor necrosis factor α
- Thyroid Hormone Transport and Metabolism
- Serum Binding Proteins

T_4 is secreted from the thyroid gland in about twentyfold excess over T_3. Both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG); transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or TBPA); and albumin. The plasma-binding proteins increase the pool of circulating hormone, delay hormone clearance, and may modulate hormone delivery to selected tissue sites.

The concentration of TBG is relatively low (1–2 mg/dL), but because of its high affinity for thyroid hormones (T_4 > T_3), it carries about 80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (~3.5 g/dL), and it binds up to 10% of T_4 and 30% of T_3.

TTR carries about 10% of T_4 but little T_3.


Medscape
T4
Type I Deiodinase
Type II Deiodinase
5'-iodinase
5-iodinase
Type III Deiodinase
T3
rT3
Type I Deiodinase
Type II Deiodinase
5'-iodinase
5-iodinase
Type III Deiodinase
T2
Source: Lab Med © 2010 American Society for Clinical Pathology

Characteristics of Circulating T_4 and T_3

Hormone Property	**T_4**	**T_3**
Serum concentrations		
Total hormone	8 μg/dL	0.14 μg/dL
Fraction of total hormone in the free form	0.02%	0.3%
Free (unbound) hormone	21 x 10^{-12} *M*	6 x 10^{-12} *M*
Serum half-life	7 d	0.75 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 μg/d	32 μg/d
Intracellular hormone fraction	~20%	~70%
Relative metabolic potency	0.3	1
Receptor binding	10^{-10} *M*	10^{-11} *M*

When the effects of the various binding proteins are combined, approximately 99.98% of T_4 and 99.7% of T_3 are protein-bound. Because T_3 is less tightly bound than T_4, the fraction of unbound T_3 is greater than unbound T_4, but there is less unbound T_3 in the circulation because it is produced in smaller amounts and cleared more rapidly than T_4. The unbound, or free, concentrations of the hormones are ~2 x 10^{-11}*M* for T_4 and ~6 x 10^{-12}*M* for T_3, which roughly correspond to the thyroid hormone receptor binding constants for these hormones.

The unbound hormone is thought to be biologically available to tissues, although the discovery of megalin as a cellular transporter of protein-bound steroids raises the possibility of distinct transport systems for bound and unbound hormones. Nonetheless, the homeostatic mechanisms that regulate the thyroid axis are directed toward maintenance of normal concentrations of unbound hormones.

Deiodinases

1) T_4 may be thought of as a precursor for the more potent T_3. T_4 is converted to T_3 by the deiodinase enzymes.

2) Type I deiodinase, which is located primarily in thyroid, liver, and kidney, has a relatively low affinity for T_4.

3) Type II deiodinase has a higher affinity for T_4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland.

4) Expression of type II deiodinase allows it to regulate T_3 concentrations locally, a property that may be important in the context of levothyroxine (T_4) replacement.

5) Type II deiodinase is also regulated by thyroid hormone; hypothyroidism induces the enzyme, resulting in enhanced $T_4 \rightarrow T_3$ conversion in tissues such as brain and pituitary. $T_4 \rightarrow T_3$ conversion is impaired by fasting, systemic illness or acute trauma, oral contrast agents, and a variety of medications (e.g., propylthiouracil, propranolol, amiodarone, glucocorticoids).

6) Type III deiodinase inactivates T_4 and T_3 and is the most important source of reverse T_3 (rT_3). Massive hemangiomas that express type III deiodinase are a rare cause of hypothyroidism in infants.

THYROID HORMONE ACTION

THYROID HORMONE TRANSPORT

Circulating thyroid hormones enter cells by passive diffusion and via the monocarboxylate 8 (MCT8) transporters that were identified in patients with multiple neurologic deficits and thyroid function abnormalities (low T4, high T3, and high TSH). After entering cells, thyroid hormones act primarily through nuclear receptors, although they also stimulate plasma membrane and mitochondrial enzymatic responses

NUCLEAR THYROID HORMONE RECEPTORS

Thyroid hormones bind with high affinity to nuclear thyroid hormone receptors (TRs) α and β. Both TRα and TRβ are expressed in most tissues, but their relative expression levels vary among organs; TRα is particularly abundant in brain, kidney, gonads, muscle, and heart, whereas TRβ expression is relatively high in the pituitary and liver.

Both receptors are variably spliced to form unique isoforms. The TRβ2 isoform, which has a unique amino terminus, is selectively expressed in the hypothalamus and pituitary, where it plays a role in feedback control of the thyroid axis. The TRα2 isoform contains a unique carboxy terminus that precludes thyroid hormone binding; it may function to block the action of other TR isoforms.

Thyroid hormones (T_3 and T_4) bind with similar affinities to TRα and TRβ. However, structural differences in the ligand binding domains provide the potential for developing receptor-selective agonists or antagonists. T_3 is bound with 10–15 times greater affinity than T_4, which explains its increased hormonal potency.

Though T_4 is produced in excess of T_3, receptors are occupied mainly by T_3, reflecting $T_4 \rightarrow T_3$ conversion by peripheral tissues, greater T_3 bioavailability in the plasma, and receptors' greater affinity for T_3.

After binding to TRs, thyroid hormone induces conformational changes in the receptors that modify its interactions with accessory transcription factors.

- Laboratory Evaluation
- Measurement of Thyroid Hormones

INTRODUCTION

Over the past forty years, improvements in the sensitivity and specificity of thyroid testing methodologies have dramatically impacted clinical strategies for detecting and treating thyroid disorders.

In the 1950s, only one thyroid test was available - an indirect estimate of the serum total (free + protein-bound) thyroxine (T4) concentration, using the protein bound iodine.[5]

Since 1970, technological advances in radioimmunoassay (RIA) and more recently immunometric assay (IMA) and tandem mass spectrometry methodologies have progressively improved the specificity, reproducibility and sensitivity of thyroid testing methods iodine (PBI) technique.

Currently, serum-based immunoassay and tandem mass spectrometric methods are available for measuring both total T4 (TT4) and total triiodothyronine (TT3) concentrations as well as the free hormone moeities (FT4 and FT3) [6]**.** In addition, measurements can be made of the thyroid hormone binding proteins,

Thyroxine Binding Globulin (TBG), Transthyretin (TTR)/Prealbumin (TBPA) and Albumin, as well as for the pituitary thyroid stimulator, Thyrotropin (thyroid stimulating hormone, TSH) and the thyroid hormone precursor protein, Thyroglobulin (Tg)[7]

Serum TSH (Thyroid Stimulating Hormone/Thyrotropin) Assays

The enhanced sensitivity and specificity of *TSH assays* have greatly improved laboratory assessment of thyroid function. Because TSH levels change dynamically in response to alterations of T_4 and T_3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated. With rare exceptions, a normal TSH level excludes a primary abnormality of thyroid function.

For practical purposes assays sensitive to ≤0.1 mU/L are sufficient. (The widespread availability of the TSH ICMA has rendered the TRH stimulation test obsolete, as the failure of TSH to rise after an intravenous bolus of 200–400 μg TRH has the same implications as a suppressed basal TSH measured by ICMA.)

The finding of an abnormal TSH level must be followed by measurements of circulating thyroid hormone levels to confirm the diagnosis of hyperthyroidism (suppressed TSH) or hypothyroidism (elevated TSH).

Serum TSH is now considered to be the most important thyroid test for assessing the early development of either hypo- or hyperthyroidism, because the log/linear TSH/FT4 relationship dictates that an altered TSH will be the first abnormality to appear - as soon as the pituitary registers that FT4 has changed from its genetically-determined setpoint for that particular individual.[8] It follows that the setting of the TSH reference range is critical for detecting mild (subclinical) hypo- or hyperthyroidism.

Current guidelines recommend that "TSH reference intervals should be established from the 95 percent confidence limits of the log-transformed values of at least 120 rigorously screened normal euthyroid volunteers who have:

a) No detectable thyroid autoantibodies, TPOAb or TgAb (measured by sensitive immunoassay);
b) No personal or family history of thyroid dysfunction;
c) No visible or palpable goiter and,
d) Who are taking no medications except estrogen" [9]

Recent studies have suggested that TSH increases with age and that a mild TSH elevation in elderly individuals may even convey a survival benefit, although other reports dispute this.[10]

These reports have led to the suggestion that age-specific TSH reference limits should be considered .[11] However, it appears that these mild TSH elevations may in part be related to polymorphisms of the TSH receptor and cannot be interpreted to imply that subclinical hypothyroidism per se is necessarily advantageous for elderly individuals. [12]

Thus the TSH upper reference limit for non-pregnant subjects remains a contentious issue so that it is difficult for manufacturers to cite a TSH reference range that could be universally adopted across different populations in different geographic areas.

This has led to guidelines proposing the adoption of an empiric TSH upper limit of 2.5 -3.0 mIU/L, which is in accord with the TSH interval associated with the lowest prevalence of thyroid antibodies. [13]

CLINICAL UTILITY OF TSH MEASUREMENT

i. **Ambulatory Patients:** Serum TSH normally exhibits a diurnal variation with a peak between midnight and 0400. However, because TSH testing is most commonly performed in the outpatient setting during normal daytime working hours, it is not usually influenced by the time of day of the blood draw.[14] It is well known that L-T4 absorption is highly variable and influenced by the simultaneous ingestion of food. To address this issue a recent study reported that TSH remained within the narrowest target range when the daily L-T4 dose was ingested in a fasting state, preferably before breakfast after an overnight fast.[15]

Current guidelines recommend that serum TSH be used as the first-line test for detecting both overt and subclinical hypo- or hyperthyroidism in ambulatory patients with stable thyroid status and intact hypothalamic/pituitary function. [16]

ii. **Hospitalized Patients**: Current guidelines recommend that serum TSH be used as the first-line test for detecting both overt and subclinical hypo- or hyperthyroidism in ambulatory patients with stable thyroid status and intact hypothalamic/pituitary function. [16]

Non-thyroidal illnesses can frequently alter thyroid hormone peripheral metabolism and hypothalamic/pituitary function and result in a variety of thyroid test abnormalities including both decreased and increased serum TSH levels. [17]

TOTAL THYROID HORMONE MEASUREMENTS (TT4 AND TT3)

Thyroxine (T4) circulates approximately 99.97% bound to the plasma proteins: TBG (60-75%), TTR/TBPA (15 -30%) and Albumin (~10%). In contrast, approximately 99.7% of Triiodothyronine (T3) is protein-bound, primarily to TBG.[18] Radioimmunoassays are widely available for serum total T_4 and total T_3.

Total (free + protein-bound) concentrations of the thyroid hormones (TT4 and TT3) circulate at nanomolar concentrations and are considerably easier to measure than the free hormone moieties (FT4 and FT3) that circulate in the picomolar range.

T_4 and T_3 are highly protein-bound, and numerous factors (illness, medications, genetic factors) can influence protein binding.

It is useful, therefore, to measure the free, or unbound, hormone levels, which correspond to the biologically available hormone pool. Two direct methods are used to measure unbound thyroid hormones:

1) unbound thyroid hormone competition with radiolabeled T_4 (or an analogue) for binding to a solid-phase antibody, and
2) physical separation of the unbound hormone fraction by ultracentrifugation or equilibrium dialysis.

TT4 AND TT3 REFERENCE RANGES

Although total T4 reference ranges vary to some extent depending on the methods employed, they have approximated 58 to 160 nmol/L (4.5-12.5 μg/dL) for more than four decades, serum TT3 values are method dependent to some extent with reference ranges approximating to 1.2 - 2.7 nmol/L (80 –180 ng/dL). [19] Total thyroid hormone levels are elevated when TBG is increased due to estrogens (pregnancy, oral contraceptives, hormone therapy, tamoxifen), and decreased when TBG binding is reduced (androgens, nephrotic syndrome).

Genetic disorders and acute illness can also cause abnormalities in thyroid hormone binding proteins, and various drugs [phenytoin, carbamazepine, salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs)] can interfere with thyroid hormone binding. For most purposes, the unbound T_4 level is sufficient to confirm thyrotoxicosis, but 2–5% of patients have only an elevated T_3 level (T_3 toxicosis).

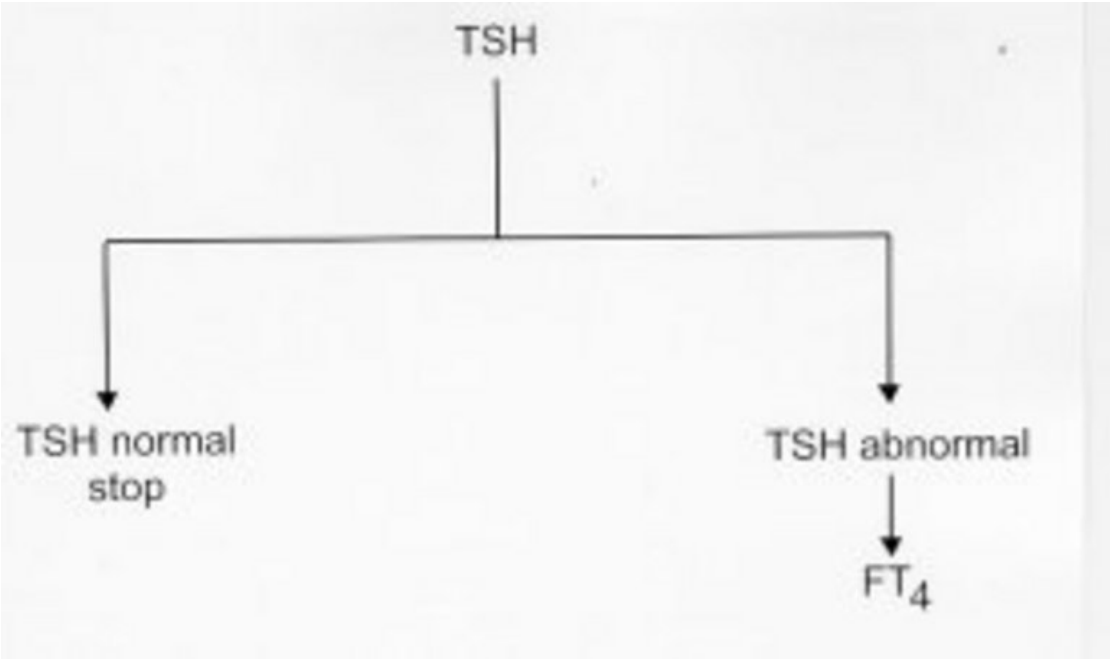
Thus, unbound T_3 levels should be measured in patients with a suppressed TSH but normal unbound T_4 levels.

Although hypothyroidism is the most common cause of an elevated TSH level, rare causes include a TSH-secreting pituitary tumor, thyroid hormone resistance, and assay artifact.

Conversely, a suppressed TSH level, particularly <0.1 mU/L, usually indicates thyrotoxicosis but may also be seen during the first trimester of pregnancy (due to hCG secretion), after treatment of hyperthyroidism (because TSH can remain suppressed for several months), and in response to certain medications (e.g., high doses of glucocorticoids or dopamine).

Importantly, secondary hypothyroidism, caused by hypothalamic-pituitary disease, is associated with a variable (low to high-normal) TSH level, which is inappropriate for the low T_4 level.

Tests for the end-organ effects of thyroid hormone excess or depletion, such as estimation of basal metabolic rate, tendon reflex relaxation rates, or serum cholesterol, are not useful as clinical determinants of thyroid function.



Clinical Utility of FT4 and FT3 Measurements

Unfortunately, the diagnostic accuracy of a free hormone determination cannot be predicted from either its methodologic classification . However, despite these shortcomings, these tests have come into common use because of their diagnostic usefulness.

FT4 and FT3 reference ranges[20]

Age Group	FT3	FT4
1 – 12 month	2.4-5.6 pg/ml	0.9 - 1.9 ng/dL
1 to 18 years	1.0 – 4.0 pg/mL	0.9 - 1.6 ng/dL
18+ years	2.3- 4.2pg/ml	0.9 - 1.6 ng/dL

These determinations were made at 25°C, when testing is performed at 37°C both T4 and FT3 values were reported as 1.5 fold higher . It is now recommended that FT4 and FT3 testing be performed at 37°C[21]

Evaluation of Thyroid Function in Health and Disease

The possibility of thyroid disease is considered when signs or symptoms suggest hyper- or hypothyroidism or some physical abnormality of the thyroid gland. Evaluation of the patient should include a thorough history and physical examination.

Since most thyroid diseases require prolonged periods of treatment, it is crucial that a firm diagnosis be established before embarking on such a program. Further, a number of medications, in particular those used in the treatment of thyroid disease, may alter the results of thyroid function tests in such a way that reinvestigation after therapy has begun may provide ambiguous results.

EVALUATION BY LABORATORY TESTS

During the past three decades, clinical thyroidology has witnessed the introduction of a plethora of diagnostic procedures. These laboratory procedures provide greater choice, sensitivity, and specificity which have enhanced the likelihood of early detection of occult thyroid diseases presenting with only minimal clinical findings or obscured by coincidental nonthyroid diseases.

They also assist in the exclusion of thyroid dysfunction when symptoms and signs closely mimic a thyroid ailment. Thyroid tests can be classified into broad categories according to the information they provide at the functional, etiologic, or anatomic levels.

1) Tests that directly assess the level of the gland activity and integrity of hormone biosynthesis. These tests such as thyroidal radioiodide uptake and perchlorate discharge are carried out in vivo.
2) Tests that measure the concentration of thyroid hormones and their transport in blood. They are performed in vitro and provide indirect assessment of the level of the thyroid hormone dependent metabolic activity.
3) Another category of tests attempts to more directly measure the impact of thyroid hormone on peripheral tissues. Unfortunately, tests available to assess this important parameter are nonspecific, since they are often altered by a variety of nonthyroidal processes.
4) The presence of several substances, such as thyroid autoantibodies, usually absent in healthy individuals, are useful in establishing the etiology of some thyroid illnesses.

5) Invasive procedures, such as biopsy, for histological examination or enzymatic studies are occasionally required to establish a definite diagnosis. Gross abnormalities of the thyroid gland, detected by palpation, can be assessed by scintiscanning and by ultrasonography.
6) The integrity of the hypothalamo-pituitary-thyroid axis can be evaluated by (a) the response of the pituitary gland to thyroid hormone excess or deficiency; (b) the ability of the thyroid gland to respond to thyrotropin (TSH); and (c) the pituitary responsiveness to thyrotropin-releasing hormone (TRH). These tests are intended to identify the primary organ affected by the disease process that manifests as thyroid dysfunction; in other words, primary (thyroid), secondary (pituitary), or tertiary (hypothalamic) malfunction.
7) Lastly, a number of special tests will be briefly described. Some are valuable in the elucidation of the rare inborn errors of hormone biosynthesis, and others are mainly research tools.

Tests of Thyroid Function and Aids in the Diagnosis of Thyroid Diseases

In Vivo Tests of Thyroid Gland Activity and Integrity of Hormone Synthesis and Secretion	Tests Related to Cardiovascular Function
Thyroidal Radioiodide Uptake (RAIU)	
Early Thyroid RAIU and 99mPertechnetate Uptake Measurements	Miscellaneous Biochemical and Physiologic Changes Related to the Action of Thyroid Hormone on Peripheral Tissues
Perchlorate Discharge Test	Measurement of Substances Absent in Normal Serum
Saliva to Plasma Radioiodide Ratio	Thyroid Autoantibodies
Measurement of Hormone Concentration and Other Iodinated Compounds and Their Transport in Blood	Thyroid-Stimulating Immunoglobulins (TSI)
Measurement of Total Thyroid Hormone Concentration in Serum	Thyroid Stimulation Assays
Iodometry	Standard in vivo Mouse Bioassay (LATS)
Radioligand and Immunometric Assays	In vitro Bioassays (animal or human tissue

	and recombinant TSH Receptor)
	Thyrotropin Binding Assays
TT4	
	Thyroid Growth-Promoting Assay
TT3	
Measurement of Total and Unsaturated Thyroid Hormone-Binding	Other Substances with Thyroid-Stimulating Activity
Capacity in Serum	Exophthalmos-Producing Substance (EPS)
In vitro Uptake Tests	Tests of Cell-Mediated Immunity (CMI)
TBG Measurement	Anatomic and Tissue Diagnoses
Estimation of Free Thyroid Hormone Concentration	Thyroid Scintiscanning
Dialysable T4 and T3 by Isotopic Equilibrium	Radioiodide and 99mPertechnitate Scans
Free T4 and T3 Index Methods	Other Isotope Scans
Estimation of FT4 and FT3 by TBG Measurement	Fluorescent Scans

Two-step Immunoassays	Ultrasonography
Analogue (one-step) Immunoassays	X-Ray and Related Procedures
Measurements of Iodine-Containing	Computed Tomography (CT Scanning)
Hormone Precursors and Products of	Angiography
Degradation	Lymphography
3.3',5'-triiodothyronine of Reverse T3 (rT3)	
	Thermography
3,5,-diiodothyronine (3,5-T2)	
3,3',-diiodothyronine (3,3'-T2)	Magnetic Resonance Imaging (MRI)
3',5',-diiodothyronine (3',5',-T2)	Biopsy of the Thyroid Gland
	Core Biopsy (Open od Closed)

EFFECTS OF THYROID HORMONE ON CARDIAC FUNCTION

The cardiovascular manifestations of thyroid hormone excess, including tachycardia, a widened pulse pressure, a brisk carotid and peripheral arterial pulsation, a hyperkinetic cardiac apex, and loud first heart sound have long been recognized and are a cornerstone for clinical diagnosis.[22] Heart rate is an important mechanism for the regulation of cardiac output.

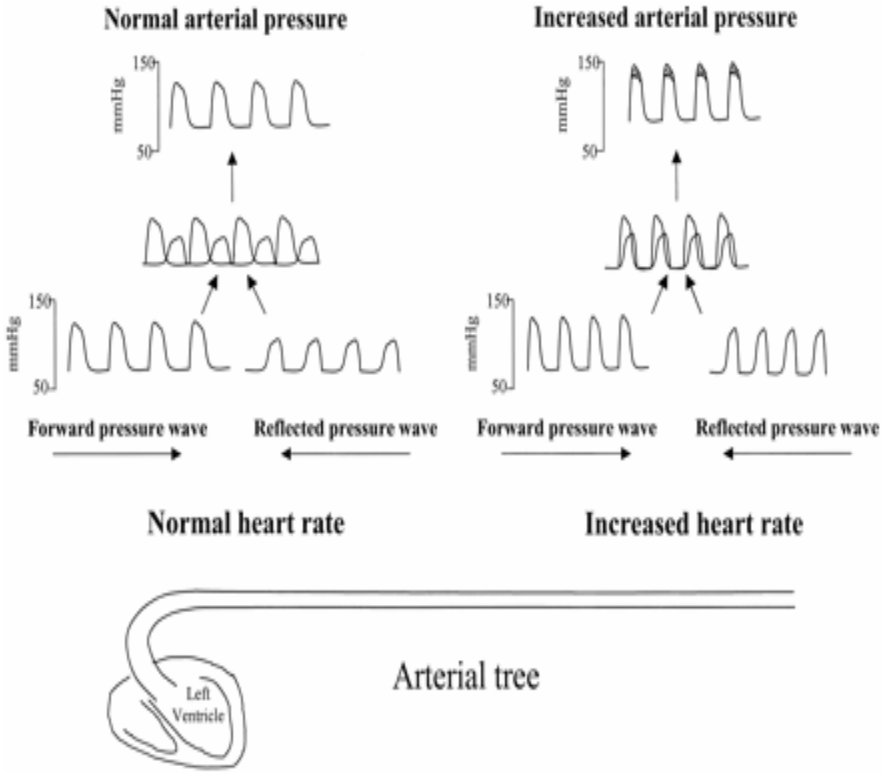
Apart from determining the rate of cardiac ejection, it affects both systolic and diastolic function. An accelerated heart rate increases the minute stroke work at any given level of cardiac preload—a finding consistent with improved myocardial contractility (force-frequency relation) [23] A high heart rate also increases the rate of myocardial relaxation, thus improving early cardiac filling (lusitropic effect) [24]

However, acceleration of the frequency of cardiac contraction does not increase cardiac performance if preload is not augmented or, at least, maintained constant. Pacing-induced increase in contraction frequency generally reduces preload and stroke volume, so that cardiac output remains constant [25].

On the other hand, an increased heart rate reduces diastolic filling time and, thus, leads to greater dependence on atrial systole. This explains the important pathophysiologic impact of atrial fibrillation on cardiac performance. Interestingly, heart rate may also affect peripheral hemodynamics.

Studies of atrially paced normal subjects have demonstrated that an increase in the frequency of cardiac contraction reduces the "dynamic" compliance of the arterial

tree and augments arterial pressure.This effect probably results from altered timing of the reflected pressure wave from the peripheral arterial tree consequent to the reduction in absolute duration of systole. That is, as systolic time lessens because of increased heart rate, the reflected pressure wave returning from the peripheral arterial tree would be added to and so enhance the forward pressure wave, thereby increasing blood pressure[26 27 28]



Potential effect of the increase in heart rate on arterial pressure in hyperthyroid patients.

Thyroid hormone has a consistent positive chronotropic effect, and resting sinus tachycardia is the most common cardiovascular sign of human hyperthyroidism . The increase in heart rate does not remain constant during 24 h; rather, circadian variation is preserved and is even more pronounced than in normal subjects. [29]

An increased incidence of atrial fibrillation has also been consistently reported in patients with overt hyperthyroidism . The increase in chronotropism and

batmotropism in hyperthyroid patients is probably caused by unbalanced sympatho-vagal tone due to a relative rather than an absolute adrenergic overdrive.[30]

This interpretation is strengthened by the observation that both catecholamine metabolism and adrenergic cardiovascular responsiveness do not differ substantially from normal in patients with hyperthyroidism. On the other hand, the close correlation between thyroid hormone level and night heart rate in hyperthyroid patients, which is least influenced by sympathetic tone, suggests that thyroid hormone may directly affect sino-atrial node firing.[31 32 33]

THYROID HORMONE AND PRELOAD

Preload is the hemodynamic force exerted on the ventricular wall during filling and, thus, corresponds to ventricular end-diastolic wall stress or tension sensu strictu. It contributes greatly to the determination of ventricular end-diastolic volume and modulates myocardial performance significantly (i.e. it governs the extent and velocity of wall shortening).

Thus, preload plays a major role in regulation of the stroke volume of the heart (Frank-Starling mechanism). Indeed, it is the most efficient mechanism by which cardiac output is adjusted to the peripheral metabolic demand. In the intact organism, preload is largely regulated by venous return, which, in turn, depends on systemic vascular resistance and venous tone. Total blood volume and atrial contraction may also significantly contribute to regulating cardiac preload [23]

To measure ventricular preload in the intact heart, one should simultaneously record internal dimension, wall thickness, and pressure at end-diastole, the latter being measured by means of invasive methodology (cardiac catheterization). Alternatively,

given normal ventricular size, chamber geometry (radius/wall thickness), and distensibility, and given the curvilinear shape of the ventricular diastolic pressure-volume relationship, end-diastolic internal dimension or volume are considered reliable indices of ventricular preload [23] It has yet to be established whether the impact of hyperthyroidism on cardiac preload in humans contributes to the increased left ventricular (LV) performance in humans [35 36]

Thyroid hormone has been shown to up-regulate erythropoietin secretion and, in turn, red blood cell mass, which may also contribute to the increase in total blood volume and cardiac preload [35]. Despite this evidence, the finding of unchanged or only marginally increased LV end-diastolic dimension or volume in hyperthyroidism has been invoked in support of the view that the Frank-Starling mechanism is not implicated in augmenting cardiac performance [37 38]

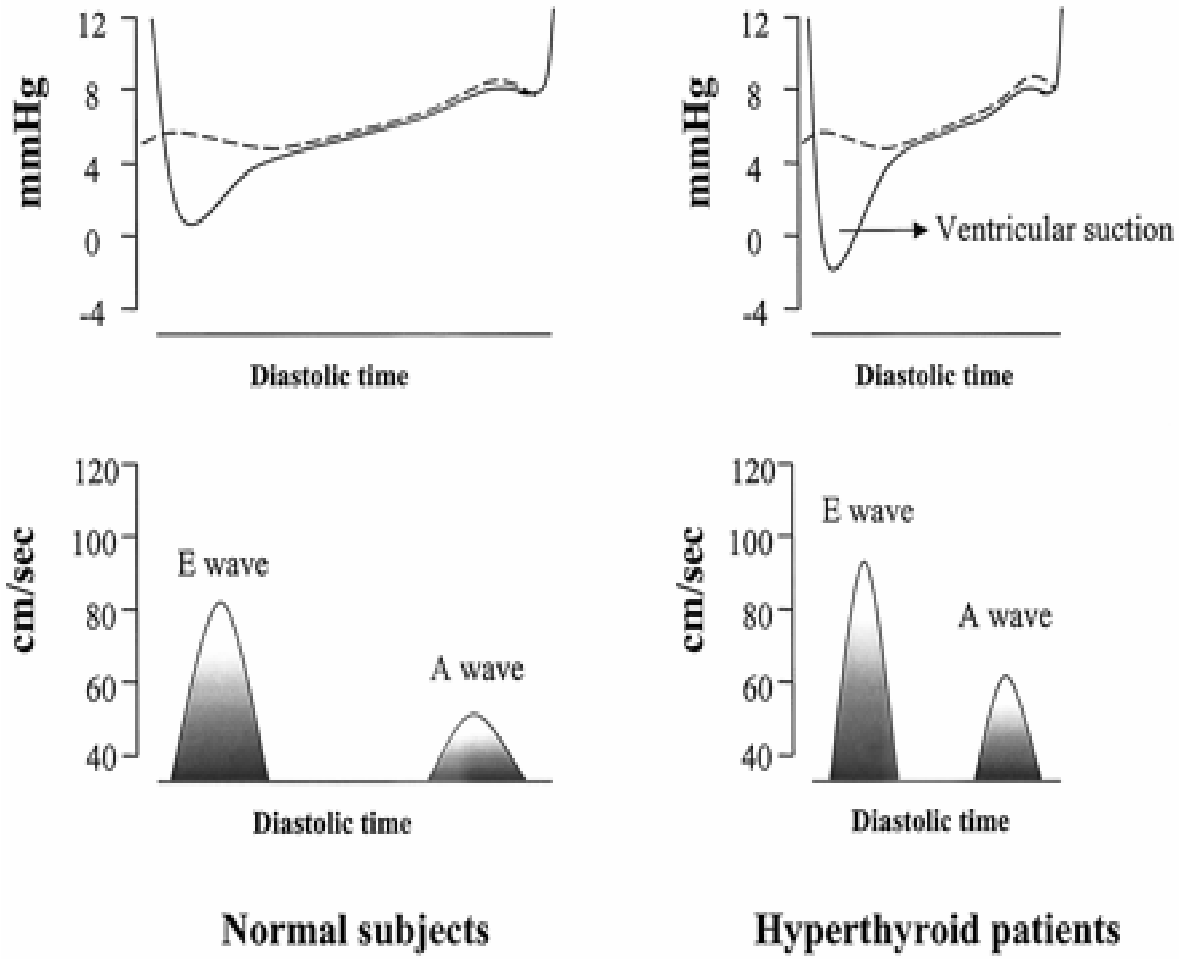
However, the augmented heart rate, as occurs in hyperthyroidism, would be expected to reduce ventricular end-diastolic dimension or volume if preload was not increased, given the inverse relationship between the two variables [39] Thus, the normal or marginally increased end-diastolic dimension or volume reported in the above-cited studies should be considered indicative of an effective increase in preload. This is supported by the finding that end-diastolic volume was higher in hyperthyroid patients than in normal subjects atrially paced at the same heart rate [41]. Further evidence for increased preload in hyperthyroidism is provided by the consistent increase in indices of early LV filling, and by the faster LV relaxation independent of the effect of heart rate and catecholamines [39.]

In fact, increased indices of early transmitral peak flow velocity and shortened LV isovolumic relaxation time in hyperthyroid patients [39 40] may reflect greater

venous return, which leads to an increased proto-diastolic transmitral pressure gradient (due to increased atrial pressure) and earlier mitral valve opening.

Alternatively, the shorter isovolumic relaxation time may be due to improved diastolic function per se, which, in turn, would allow the increased venous return to be accommodated without relevant changes in filling pressure.

By accentuating the isovolumic intracavity pressure decay, the increased rate of ventricular relaxation enhances ventricular suction [43] [44]. Accordingly, the greater early atrioventricular pressure gradient in hyperthyroid patients could be sustained by enhanced ventricular suction rather than by a relevant increase in atrial pressure. This interpretation is supported by the observation of comparable values of LV end-diastolic volume and pressure in hyperthyroid patients and normal subjects [45]



Effect of ventricular suction on the atrio (*dotted line*)-ventricular (*solid line*) pressure gradient and transmitral Doppler flow velocimetry.

THYROID HORMONE AND AFTERLOAD

Afterload is the hemodynamic force exerted on the ventricular wall during ejection, corresponding, therefore, to end-systolic wall stress or tension sensu strictu. It contributes to the determination of ventricular end-systolic volume and modulates myocardial performance significantly (*i.e.* it governs the extent and velocity of wall shortening).

Thus, afterload is a determinant of the stroke volume of the heart (force-velocity relation) in that it provides a crucial servomechanism for the functional coupling of the cardiac pump to the arterial system. In the intact organism, afterload is largely regulated by arterial pressure (vascular afterload), which, in turn, depends on interaction between the steady (systemic vascular resistance) and pulsatile (global arterial compliance, aortic characteristic impedance, and indices of wave propagation and reflection) components of arterial load. Changes in ventricular size and chamber geometry may also affect ventricular afterload (cardiac afterload) [23]

Afterload in the intact heart can be measured by simultaneous recording of internal dimension, wall thickness, and pressure at end-systole, which requires cardiac catheterization. Alternatively, given the correlation between systolic arterial pressure and end-systolic ventricular pressure, end-systolic wall stress estimated from cuff sphygmomanometer measurements is a reliable measure of ventricular afterload [23].

In many review articles; on the effects of thyroid hormone on the cardiovascular system, ventricular after load has long been reported to be reduced in hyperthyroid patients [45 47].

THYROID HORMONE AND MYOCARDIAL CONTRACTILITY

The term "myocardial contractility" refers to the intrinsic property of the cardiac muscle to do work, that is "the potential to do work" [19]. Thus, it corresponds to the performance of the heart independent of the effect of heart rate and/or loading status *sensu strictu*. By contrast, the term "LV systolic function" represents the aggregate effect of all the mechanisms that control cardiac performance (heart rate, preload, afterload, and myocardial contractility). In hyperthyroid patients there is a consistent improvement in LV systolic function at rest [48 49]

There are two schools of thought as to how this finding should be interpreted in terms of myocardial contractility. Controversy is fueled by the different importance given to changes in heart rate and cardiac loading conditions. In studies in which preload and/or afterload were considered to be substantially unaffected by thyroid hormone excess, the enhancement of LV systolic function, independent of the effect of heart rate, was viewed as the result of a mandatory increase in the level of myocardial contractility [22 36 40 47] .

By contrast, in studies in which thyroid hormone was thought to have a pronounced effect on heart rate and peripheral circulation, the presence of an effective increase in myocardial contractility was considered too simplistic [29 48]

Thyroid hormone and cardiac performance: integrated responses

The concept that emerges from this review is that the increase in heart rate and preload could play a major role in augmenting LV performance in human hyperthyroidism, thus reinforcing the notion that the hyperkinetic cardiovascular state in human hyperthyroidism is an adaptive response to the increase in the peripheral metabolic demand promoted by thyroid hormone [51 52].

By reducing systemic vascular resistance, thyroid hormone would shift blood from the arterial to the venous compartment of the vascular system, thus unloading the arterial tree. This effect, coupled with activation of the renin-angiotensin-aldosterone system and with increased red blood cell mass, would increase blood volume and, in turn, the venous return to the heart.

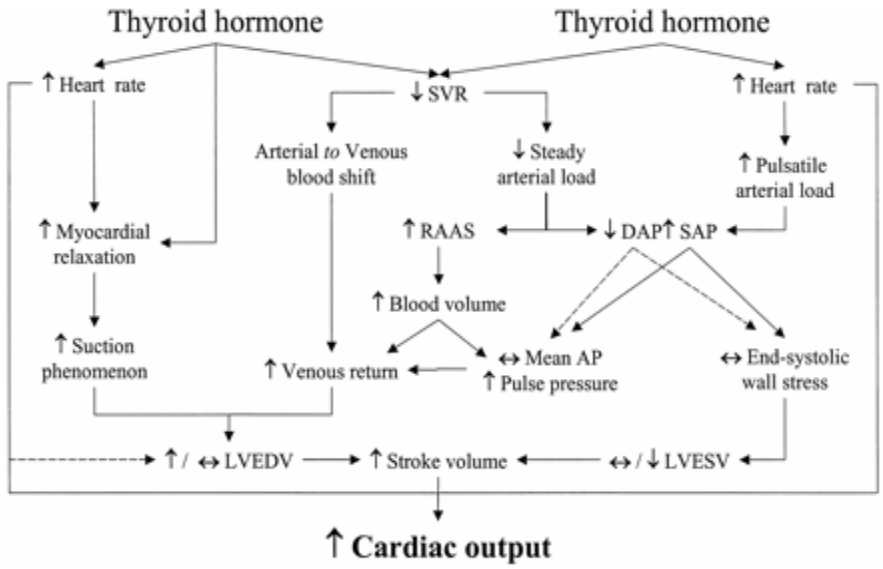
At the same time, by increasing heart rate and improving ventricular diastolic function, thyroid hormone would enhance ventricular suction, thus allowing the heart to accommodate the greater venous return without major changes in ventricular end-diastolic pressure and dimension.

This mechanism would mask the increase in cardiac preload, leading to an underestimation of the extent to which the Frank-Starling mechanism contributes to improving cardiac performance. On the other hand, by reducing the dynamic compliance of the arterial tree, the increase in heart rate would help to increase systolic arterial pressure.

As a result, by counteracting the marked reduction in diastolic arterial pressure due to the fall in systemic vascular resistance, the slight but significant increase in systolic blood pressure would, in turn, maintain mean arterial pressure and increase

pulse pressure. Consequently, the increased LV performance would be converted into the typical hyperdynamic cardiocirculatory state.

Therefore, although the augmented LV performance is important in determining the high output state in human hyperthyroidism, the alterations in the peripheral circulation seem to be of at least equal significance. That is, if the increase in LV pump function is necessary to sustain the high output state, changes in peripheral circulation must act in concert to develop and maintain the hyperkinetic cardiovascular state.



Pathophysiological paradigm of the mechanisms by which at-rest cardiac output is increased in human hyperthyroidism (dotted line, inhibitory action). SVR, Systemic vascular resistance; RAAS, renin-angiotensin-aldosterone system; DAP, diastolic arterial pressure; SAP, systolic arterial pressure; AP, arterial pressure; LVEDV, LV end-diastolic volume; LVESV, LV end-systolic volume.

CARDIOVASCULAR EFFECTS OF HYPOTHYROIDISM

Hypothyroidism is characterized by a decrease in oxygen and substrate utilization by all the major organ systems of the body. As a result, the demands for cardiac output decrease; in addition, hypothyroidism directly alters cardiac function through changes in myocyte-specific gene expression [53] Pulse rate and stroke volume are diminished in hypothyroidism, and cardiac output is accordingly decreased, often to one-half the normal value [54].

Myocardial contractility is reduced, but there is also a steep decline in the circulatory load, so that the circulation rarely fails until very late in the disease [53]. The speed of shortening is slowed, but the total force is not much modified. [54]. Myocardial adenyl cyclase levels are reduced [55].

The decrease in pulse rate occurs more or less in parallel with that of the metabolism. Stroke volume is reduced more than pulse rate at any given level, and is therefore the major determinant of the low cardiac output.

Since the reduction in cardiac output is usually proportional to the decreased oxygen consumption by the tissues, the arteriovenous (AV) oxygen difference is normal or may be slightly increased.

Slow peripheral circulation, and therefore more complete extraction of oxygen, as well as anemia, may be responsible for the increased AV oxygen difference. Myocardial oxygen consumption is decreased, usually more than blood supply to the myocardium, so that angina is infrequent. In some patients a reduction in cardiac output greater than the decline in oxygen consumption indicates specific cardiac damage from the myxedema [57].

Venous pressure is normal, but peripheral resistance is increased. Restoration of the euthyroid state normalizes peripheral vascular resistance. Changes in peripheral vascular resistance are not related to plasma adrenomedullin, but altered atrial natriuretic peptide secretion and adrenergic tone may contribute [57].

Central arterial stiffness is increased in hypothyroidism [58], and arterial blood pressure is often mildly increased. It varies widely, but diastolic hypertension is usually restored to normal after treatment [59 60]. The heart in hypothyroidism has been a focus of much controversy.

The term Myxodemherz was introduced by Zondek in 1918 [61]. It embraced dilatation of the left and right sides of the heart, slow, indolent heart action with normal blood pressure, and lowering of the P and T waves of the electrocardiogram. Zondek found that after treatment with thyroid hormone there was a return of the dilated heart to somewhere near normal size, a more rapid pulse without change in blood pressure, and gradual return of the P and T waves to normal. These findings have been confirmed and extended. Indeed, occasional severely hypothyroid patients without underlying heart disease have congestive heart failure or low cardiac output reversed by thyroid hormone administration [59 60 61].

Therefore, congestive heart failure or impaired cardiac output relative to metabolic needs can be caused by hypothyroidism. Microscopic examination discloses myxedematous changes of the myocardial fibers. The cause of the cardiac enlargement has been disputed. Clearly, it is not due to hypertrophy alone, since it would not disappear so rapidly with treatment. One factor may be a decrease in contractility of the heart muscle. This decrease would require a lengthening of muscle fibers in order to perform the required work.

Disappearance of interstitial fluid alone could account for only part of the observed schrinkage. Altered myosin synthesis is also important. Gordon long ago called attention to the occurrence of pericardial effusion in myxedema and explained the increase in the transverse diameter of the heart shadow on this basis. Effusion must frequently play a role in the increase in the size of the heart shadow, but it has amazingly little effect on cardiodynamics. Thepresence of fluid may be reflected in the right ventricular pressure contour, but tamponade, although reported, is rare [62 63.]

Effusions of the pericardium, pleura, and peritoneum are common findings in hypothyroidism the protein of the effusion may be high or in the range of transudates. The hypothyroid heart responds normally to exercise [56 58]. Graettinger et al. found that after exercise the low resting cardiac output increased normally with an increase of stroke volume and usually, of pulse rate.

Since the treatment of myxedema restores the hypothyroid heart to normal, there is apparently little permanent structural damage [63 68].

- The electrocardiogram reveals characteristic changes [56 58 63 69].
- The rate is slow and the voltage is low.
- The T waves are flattened or inverted. Axis deviation,
- an increased P-R interval, and widened QRS complexes and prolonged QT interval are seen, but these signs are not diagnostic of myxedema.
- The pattern reverts toward normal with treatment,

The rare occurrence of complete heart block complicated by Adams-Stokes attacks, with reversion to sinus rhythm after treatment with thyroid hormone, has been reported as has ventricular tachycardia [65 66]. Changes resembling those of ischemic heart disease may be found during exercise: they may indicate an intrinsic anoxia rather than organic narrowing of the coronary vessels.

THE GLOBAL BURDEN OF DISEASE [70]

Non-communicable diseases now cause almost half of the burden of disease in low- and middle-income countries. Almost one half of the disease burden in low- and middle-income countries is now from non-communicable diseases.

Ischemic heart disease and stroke are the largest sources of this burden, especially in the low- and middle-income countries of Europe, where cardiovascular diseases account for more than one quarter of the total disease burden.

The two leading causes of death – ischemic heart disease and cerebrovascular disease – remain among the top six causes of burden of disease.

DISABILITY-ADJUSTED LIFE YEAR (DALY)

WORLD

- Ischaemic Heart Disease 62.6(millions) 4.1(% of total DALY)
- Cerebrovascular disease 46.6(millions) 3.1(% of total DALY)

Ishemic Heart Disease and Cerebrovascular disease account for nearly 100 million people and nearly 7% of all causes of diseases, coming 4^{th} and 6^{th} respectively in the leading causes of disease burden preceded only by communicable diseases (which accounts for nearly 20% of total burden).

MIDDLE-INCOME COUNTRIES

- Ischaemic heart disease 28.9(millions) 5.0(% of total DALY)
- Cerebrovascular disease 27.5(millions) 4.8(% of total DALY)
- In middle income countries they are the 2^{nd} and 3^{rd} leading cause of burden of disease

LOW-INCOME COUNTRIES

- Ischaemic heart disease 26.0(millions) 3.1(% of total DALY)
- In low income countries it`s 9th, preceded only by communicable diseases.

HIGH-INCOME COUNTRIES

- Ischaemic heart disease 7.7(millions) 6.3(% of total DALY)
- Cerebrovascular disease 4.8(millions) 3.9(% of total DALY)
- In high income countries they are at 2nd and 3rd place respectively

SOUTH-EAST ASIA REGION

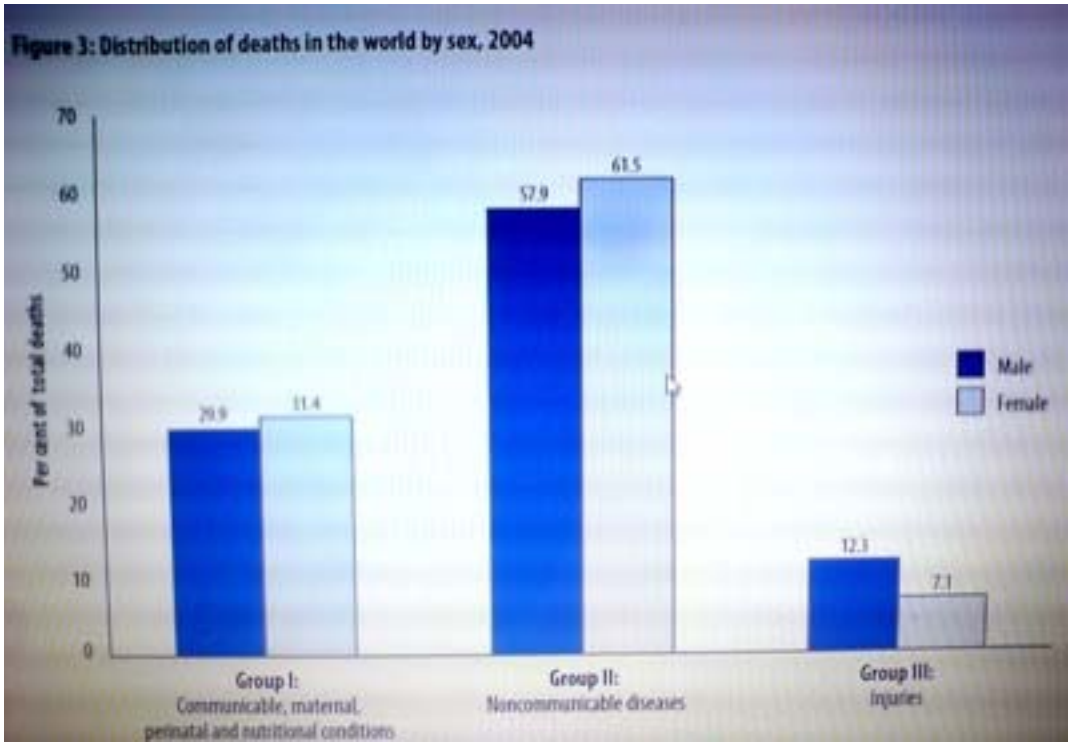
- Ischaemic heart disease 21.6 millions) 4.9(% of total DALY)
- Cerebrovascular disease 9.6 millions) 2.2(% of total DALY)
- In our part of the world they are at 3rd and 10th place respectively.
- The Growing Burden of Non-communicable Disease
- The burden of non-communicable diseases now accounts for nearly half of the global burden of disease (all ages).
- Surprisingly, almost 45% of the adult disease burden in low- and middle-income countries globally is now attributable to non-communicable disease. Population ageing and changes in the distribution of risk factors have accelerated the non-communicable disease share of total disease burden in many developing countries.

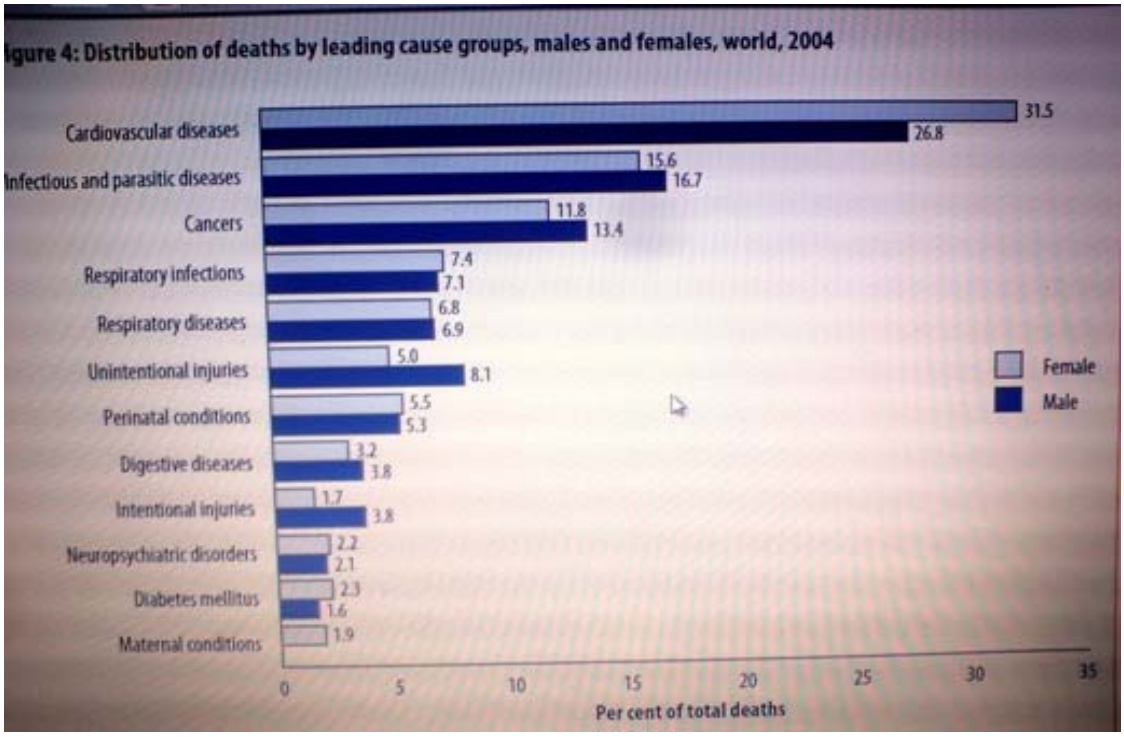
Non-communicable diseases dominate the disease burden of high-income countries, and in the past they have often been seen as a health priority mainly for high-income countries. In part this reflects the older population structure of the high-income countries, because non-communicable disease risks generally increase with age. If the effects of different age distributions of populations are controlled for

through age-standardization of DALY rates, it becomes apparent that non-communicable disease risks, as measured by age-standardized DALY rates, are higher in low- and middle-income countries than in high-income countries.

This is mainly due to cardiovascular diseases, principally ischemic heart disease and stroke, whose age standardized burden is substantially higher in lower middle-income countries than in high-income countries.

DISTRIBUTION OF DEATHS: SEX AND GROUP WISE





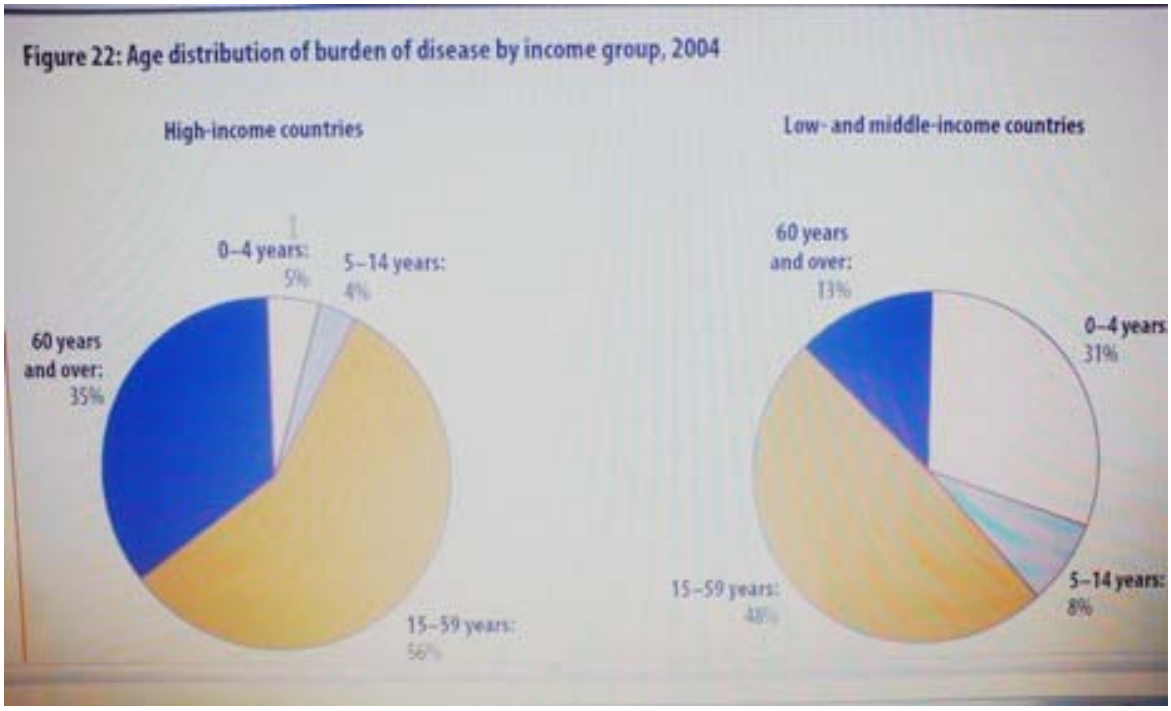
Distribution of Deaths by Leading Causes

PROJECTED BURDEN OF DISEASE IN 2030

1) By the year 2030 Ischemic heart disease and Cerebrovascular heart diseases are expected to go from 4th and 6th position up to 2nd and 4th leading cause.
2) The proportional contribution of the three major cause groups to the total disease burden is projected to change substantially.
3) Group I (communicable) causes are projected to account for 20% of total DALYs lost in 2030, compared with just fewer than 40% in 2004.
4) The non-communicable disease (Group II) burden is projected to increase to 66% in 2030, and to represent a greater burden of disease than Group I conditions in all income groups, including low-income countries.

Figure 27: Ten leading causes of burden of disease, world, 2004 and 2030

2004 Disease or injury	As % of total DALYs	Rank	Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1	1	6.2	Unipolar depressive disorders
Diarrhoeal diseases	4.8	2	2	5.5	Ischaemic heart disease
Unipolar depressive disorders	4.3	3	3	4.9	Road traffic accidents
Ischaemic heart disease	4.1	4	4	4.3	Cerebrovascular disease
HIV/AIDS	3.8	5	5	3.8	COPD
Cerebrovascular disease	3.1	6	6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7	7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8	8	2.7	Refractive errors
Road traffic accidents	2.7	9	9	2.5	HIV/AIDS
Neonatal infections and other[a]	2.7	10	10	2.3	Diabetes mellitus
COPD	2.0	13	11	1.9	Neonatal infections and other[a]
Refractive errors	1.8	14	12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	15	15	1.9	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19	18	1.6	Diarrhoeal diseases



Age wise distribution of burden of disease in High and Low income countries

MATERIAL AND METHODS

SOURCE OF DATA

Elderly patients aged 60 years and above, admitted to B.L.D.E.A's Sri B.M.Patil Medical College, Hospital and Research Center Bijapur, with cardiovascular events from October 2008 to April 2010.

INCLUSION CRITERIA

a) All elderly patients admitted with cardiovascular events.

Aged 60 years and above.

CARDIOVASCULAR EVENTS WILL INCLUDE

ARRHYTHMIA

Classified by rate (normal, tachycardia, bradycardia), or mechanism (automaticity, reentry, fibrillation). Detected by 12 lead ECG and 2-d ECHO

Congestive Heart Failure

Clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and/or function, develop a constellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy. Detected by Physical examination, 12 lead ECG, Chest XRays, 2-d ECHO

MYOCARDITIS

Inflammation of heart muscle (myocardium)

Detected by physical signs and symptoms, 12 lead ECG change, Cardiac Enzymes (CPK MB / Troponin T), 2-d ECHO, Cardiac Color Doppler, Serology if needed.

CORONARY ARTERY DISEASE

Coronary artery disease (CAD), also called coronary heart disease, is a condition in which plaque (plaque) builds up inside the coronary arteries.

Detected by physical signs and symptoms, 12 lead ECG change, Cardiac Enzymes (CPK MB / Troponin T), 2-d ECHO, and Cardiac Color Doppler

CARDIOMYOPATHY

The deterioration of the function of the myocardium. Detected by physical signs and symptoms, 12 lead ECG change, Cardiac Enzymes (CPK MB / Troponin T), 2-d ECHO, and Cardiac Color Doppler

DIASTOLIC DYSFUNCTION

Decline in performance of the ventricles of the heart during the phase of diastole. Detected by Cardiac Color Doppler

HIGH BLOOD PRESSURE (HYPERTENSION)

As per JNC 7 criteria

EXCLUSION CRITERIA

a) All elderly patients admitted being on thyroid medication

b) All elderly patients admitted with history of congenital heart disease or rheumatic heart disease.

c) All elderly patients admitted on medication like corticosteroids, amiodarone.

Lab assessment of thyroid functions status

Measurement of Circulating Thyroid Hormone Concentration

Venous blood samples drawn in fasting state were used for biochemical laboratory analysis. The laboratory examinations included estimation of total (TCHOL) and HDL cholesterol (HDL), triglycerides (TG), and glucose (GLU)

Thyroid stimulating hormone TSH, T3 and T4 was assessed using commercial fluorescent polarization immunoassay (FPIA) kits (Abbott Laboratories, Wiesbaden, Germany)

OBSERVATIONS AND RESULTS

(CHARTS AND TABLES)

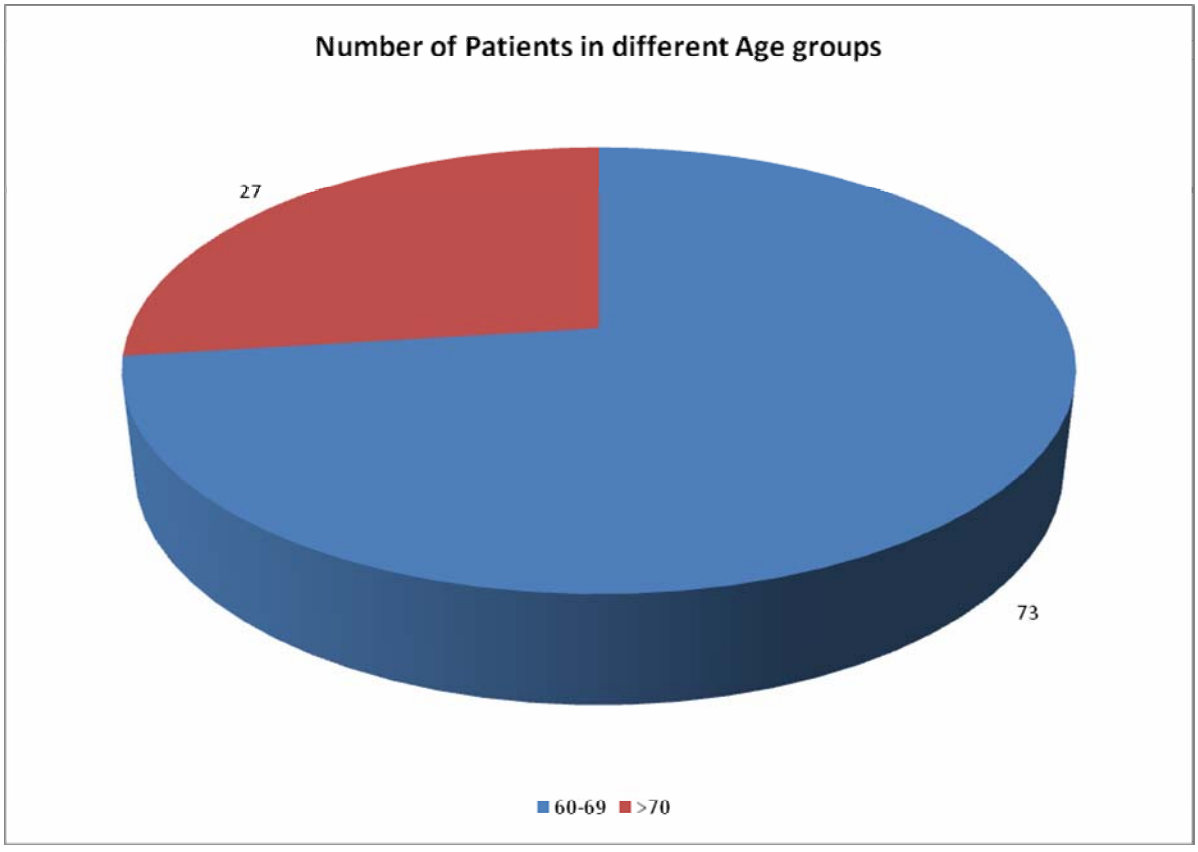
AGE DISTRIBUTION

Table No 1

Age Groups

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	60-69 years	50	72.5	72.5	72.5
	>70 years	19	27.5	27.5	100.0
	Total	69	100.0	100.0	

Graph No 1



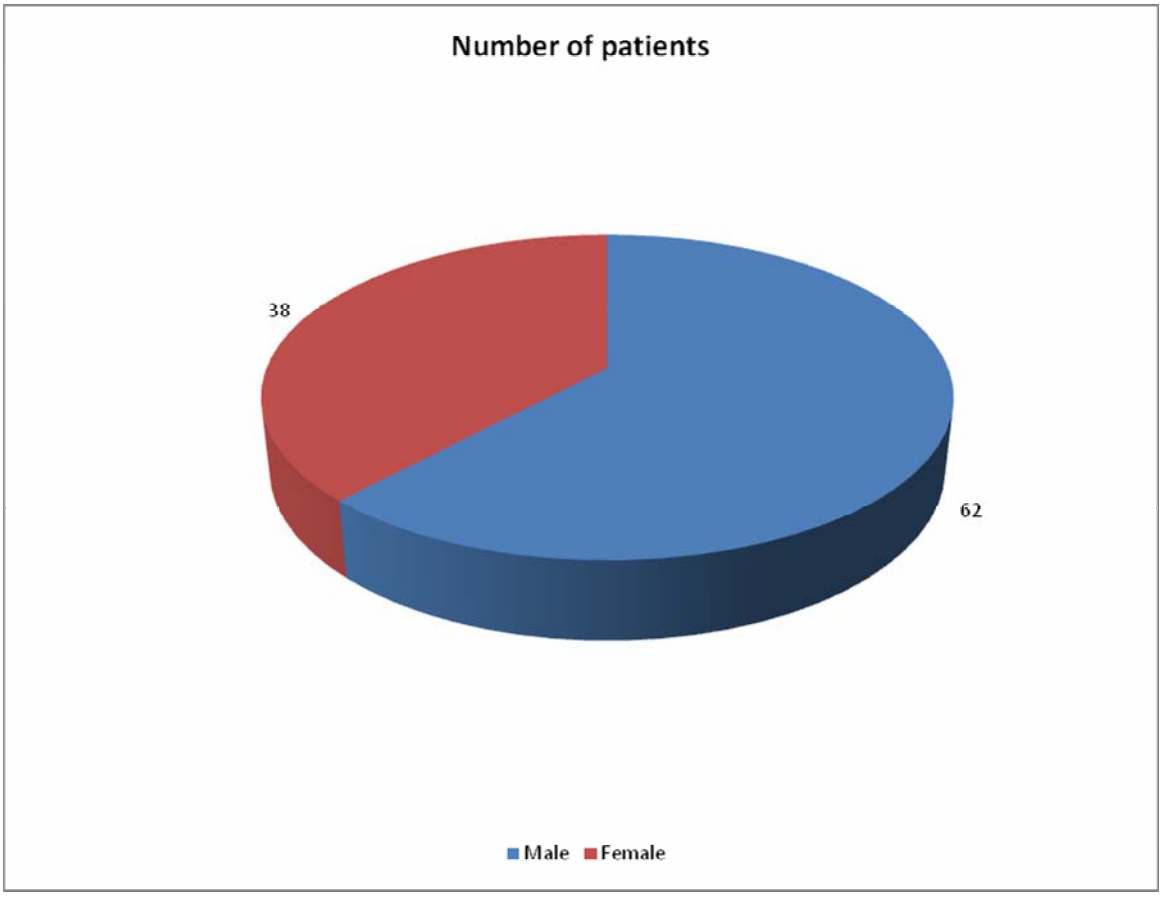
SEX DISTRIBUTION

Table No 2

Sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	43	62.3	62.3	62.3
	Female	26	37.7	37.7	100.0
	Total	69	100.0	100.0	

Graph No 2



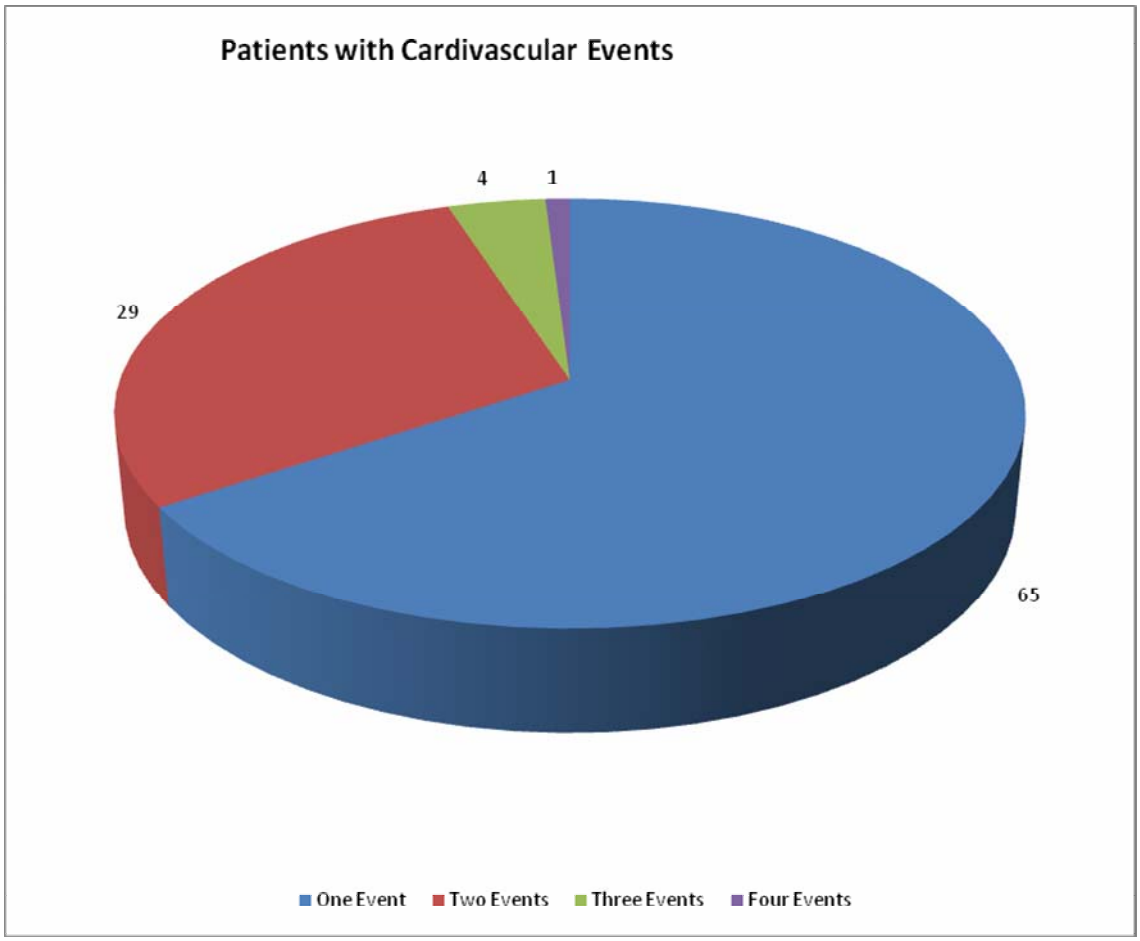
DISTRIBUTION OF CV EVENTS

Table No 3

Number of events

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	One event	45	65.2	65.2	65.2
	Two events	20	29.0	29.0	94.2
	Three events	3	4.3	4.3	98.6
	Four events	1	1.4	1.4	100.0
	Total	69	100.0	100.0	

Graph No 3



AGE WISE DISTRIBUTION OF EVENTS

Table No 4

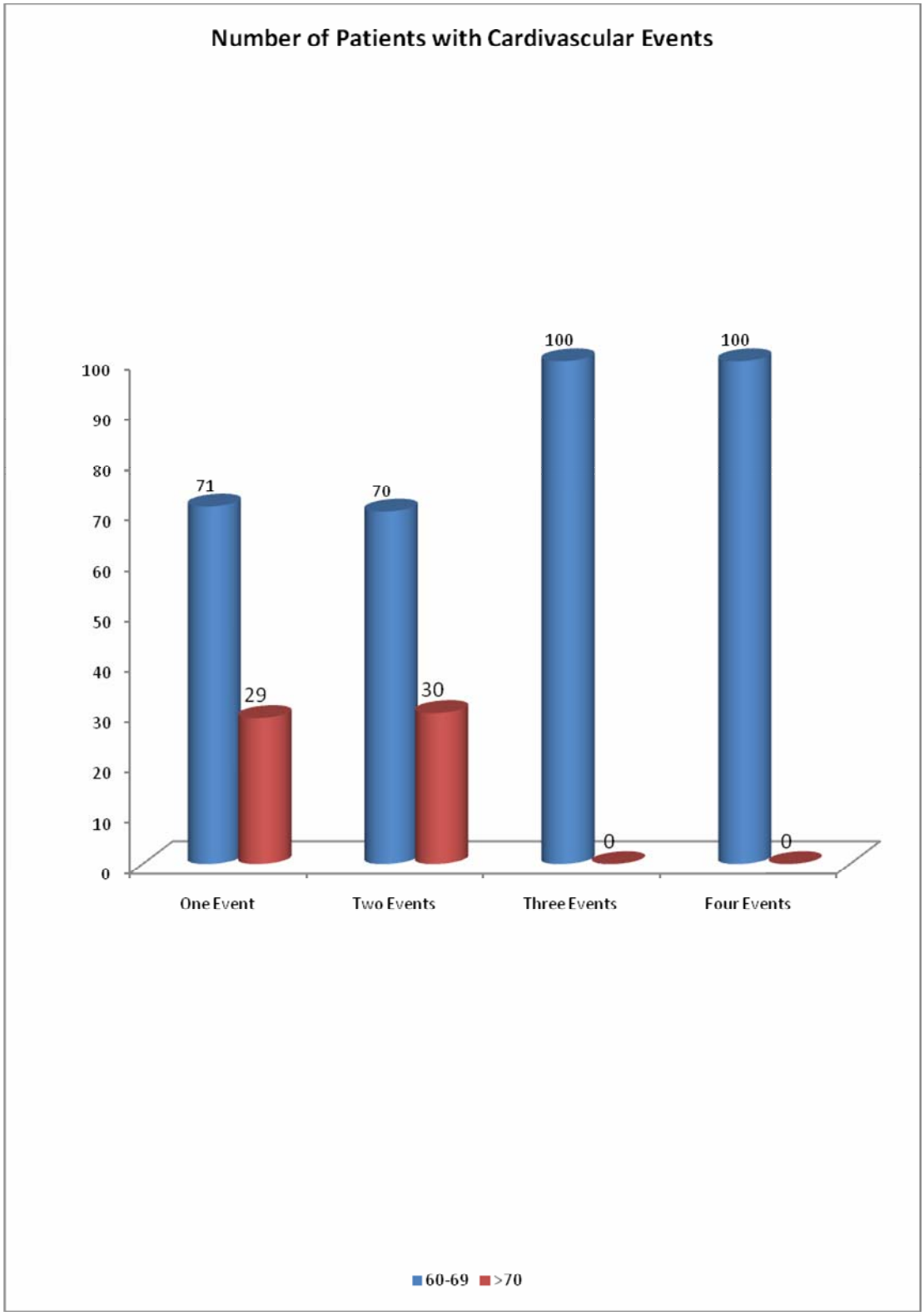
Age Groups * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Age Groups	60-69 years	Count	32	14	3	1	50
		% within Age Group	64.0%	28.0%	6.0%	2.0%	100.0%
	>70 years	Count	13	6	0	0	19
		% within Age Group	68.4%	31.6%	.0%	.0%	100.0%
Total		Count	45	20	3	1	69
		% within Age Group	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.622[a]	3	.654
Likelihood Ratio	2.677	3	.444
Linear-by-Linear Association	.676	1	.411
N of Valid Cases	69		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .28.


Number of Patients with Cardivascular Events
100
90
80
70
60
50
40
30
20
10
0
71
29
70
30
100
0
100
0
One Event
Two Events
Three Events
Four Events
60-69
>70

Graph No 4

SEX WISE DISTRIBUTION OF EVENTS

Table No 5

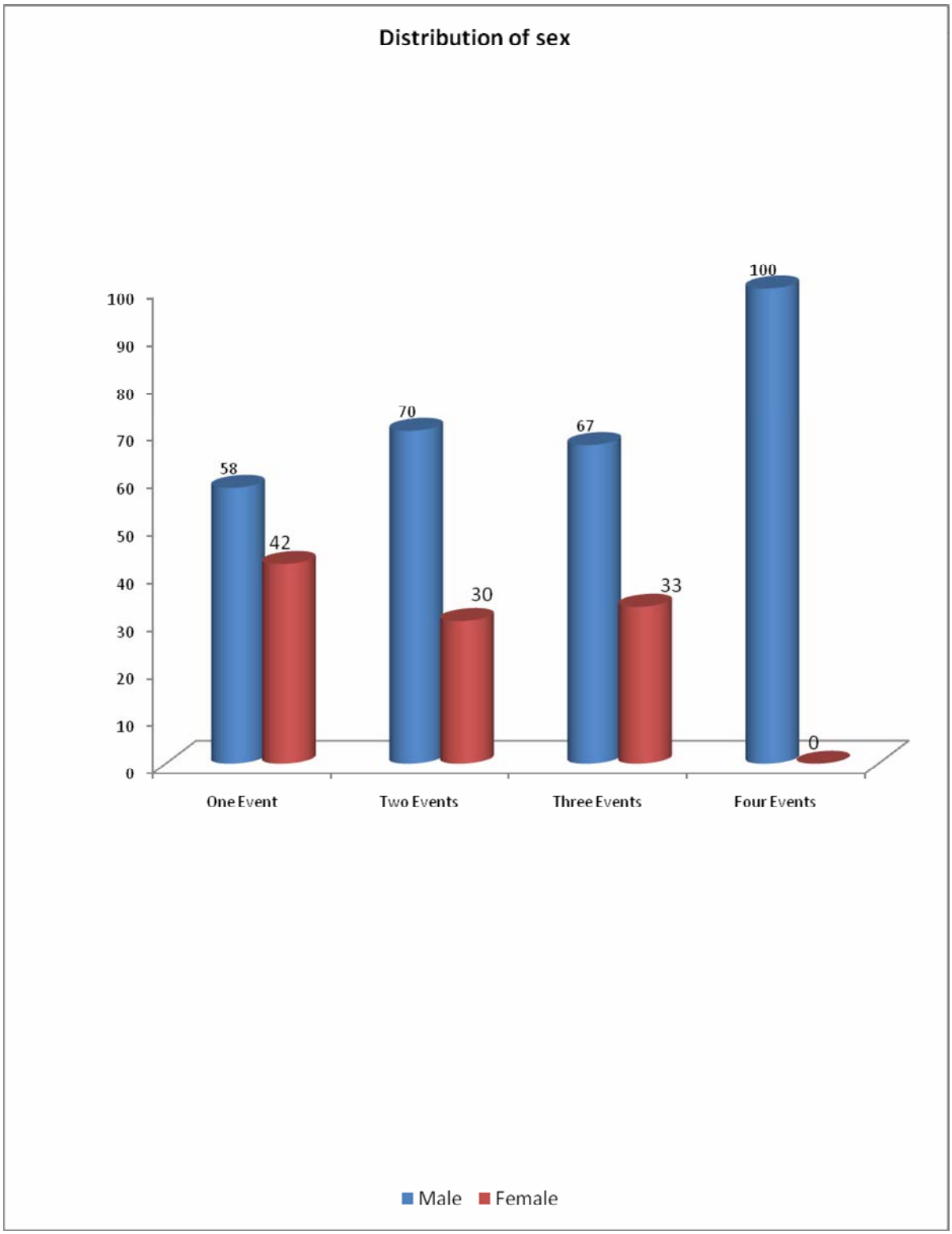
Sex * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Sex	Male	Count	26	14	2	1	43
		% within Se	60.5%	32.6%	4.7%	2.3%	100.0%
	Female	Count	19	6	1	0	26
		% within Se	73.1%	23.1%	3.8%	.0%	100.0%
Total		Count	45	20	3	1	69
		% within Se	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	1.526[a]	3	.676
Likelihood Ratio	1.879	3	.598
Linear-by-Linear Association	1.248	1	.264
N of Valid Cases	69		

a. 4 cells (50.0%) have expected count less than 5. The minimum expected count is .38.


Distribution of sex
100
90
80
70
60
50
40
30
20
10
0
58
42
70
30
67
33
100
0
One Event
Two Events
Three Events
Four Events
Male
Female

Graph No 5

PRE EXISTING HYPERTENSION AND CV EVENTS

Table No 6

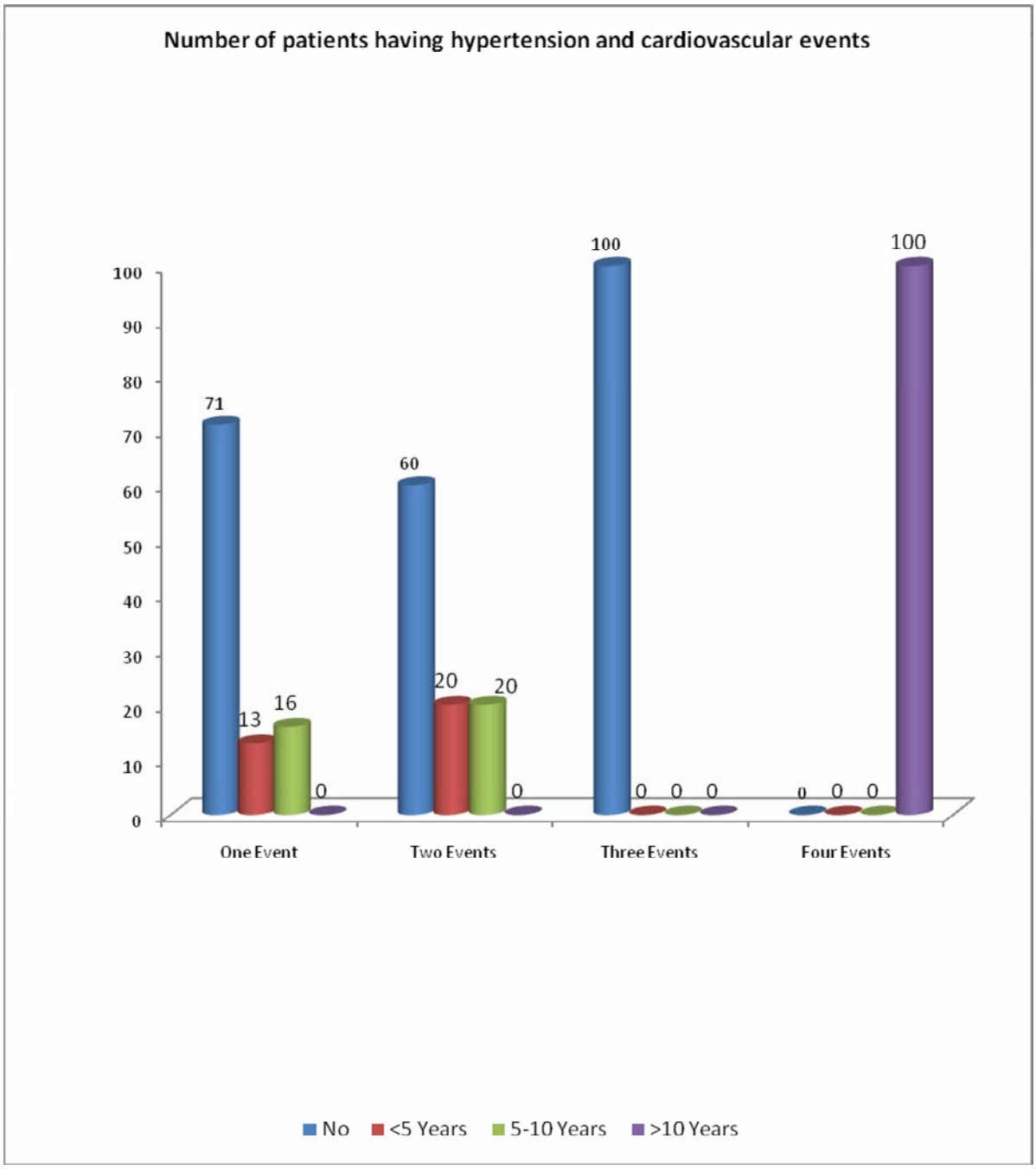
Hypertension * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Hypertensio	No	Count	32	12	3	0	47
		% within Hypertens	68.1%	25.5%	6.4%	.0%	100.0%
	<5 years	Count	6	4	0	0	10
		% within Hypertens	60.0%	40.0%	.0%	.0%	100.0%
	5-10 years	Count	7	4	0	0	11
		% within Hypertens	63.6%	36.4%	.0%	.0%	100.0%
	>10 years	Count	0	0	0	1	1
		% within Hypertens	.0%	.0%	.0%	100.0%	100.0%
Total		Count	45	20	3	1	69
		% within Hypertens	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	71.270[a]	9	.000
Likelihood Ratio	13.528	9	.140
Linear-by-Linear Association	2.064	1	.151
N of Valid Cases	69		

a. 12 cells (75.0%) have expected count less than 5. The minimum expected count is .01.


Number of patients having hypertension and cardiovascular events
100
90
80
70
60
50
40
30
20
10
0
71
13
16
0
60
20
20
0
100
0
0
0
0
0
0
100
One Event
Two Events
Three Events
Four Events
No
<5 Years
5-10 Years
>10 Years

Graph No 6

PRE EXITING DIABETES AND CV EVENTS

Table No 7

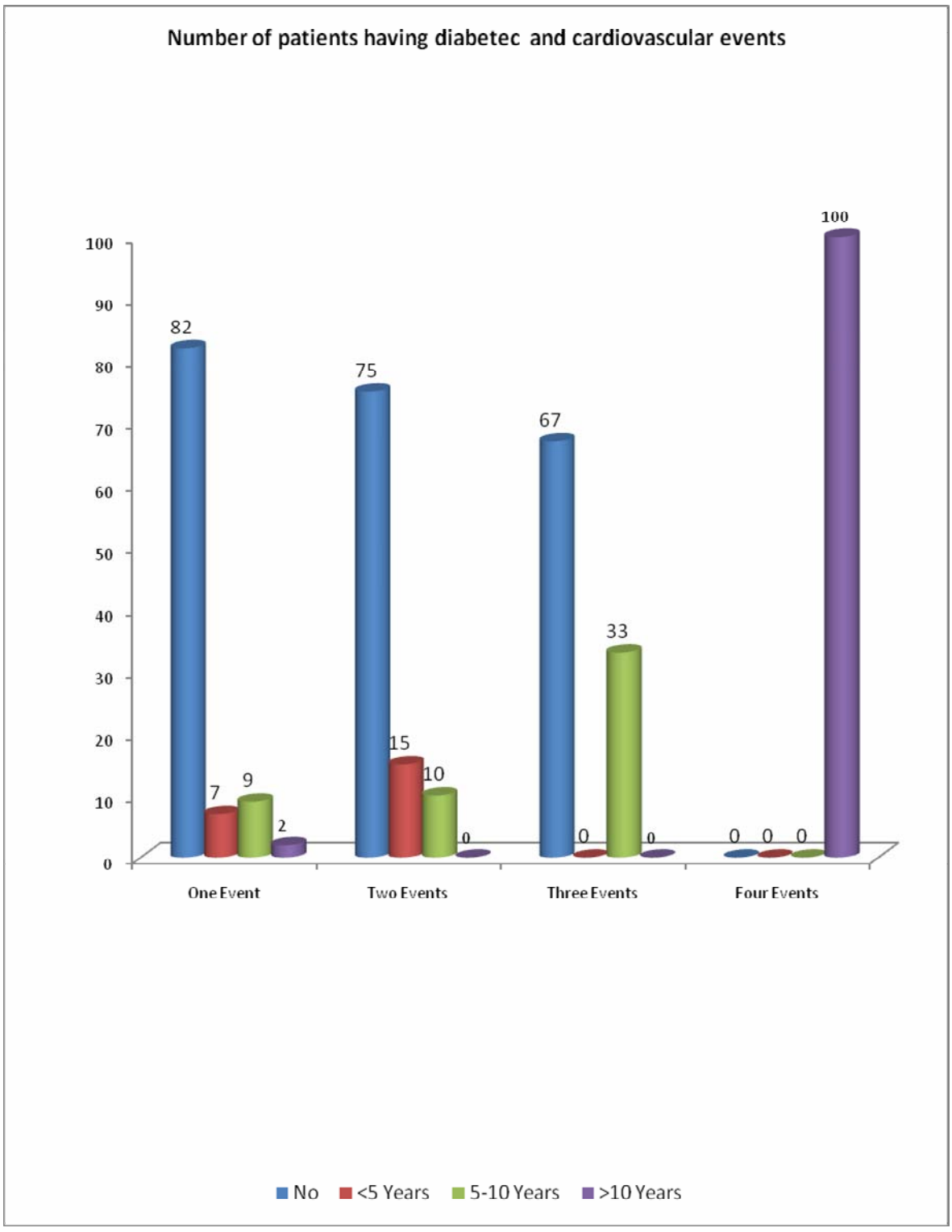
Diabetec * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Diabetec	No	Count	37	15	2	0	54
		% within Diabetec	68.5%	27.8%	3.7%	.0%	100.0%
	<5 years	Count	3	3	0	0	6
		% within Diabetec	50.0%	50.0%	.0%	.0%	100.0%
	5-10 years	Count	4	2	1	0	7
		% within Diabetec	57.1%	28.6%	14.3%	.0%	100.0%
	>10 years	Count	1	0	0	1	2
		% within Diabetec	50.0%	.0%	.0%	50.0%	100.0%
Total		Count	45	20	3	1	69
		% within Diabetec	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	37.455[a]	9	.000
Likelihood Ratio	11.228	9	.260
Linear-by-Linear Association	4.603	1	.032
N of Valid Cases	69		

a. 14 cells (87.5%) have expected count less than 5. The minimum expected count is .03.


Number of patients having diabetec and cardiovascular events
100
90
80
70
60
50
40
30
20
10
0
82
7
9
2
75
15
10
0
67
0
33
0
0
0
0
100
One Event
Two Events
Three Events
Four Events
No
<5 Years
5-10 Years
>10 Years

Graph No 7

SMOKING AND CV EVENTS

Table No 8

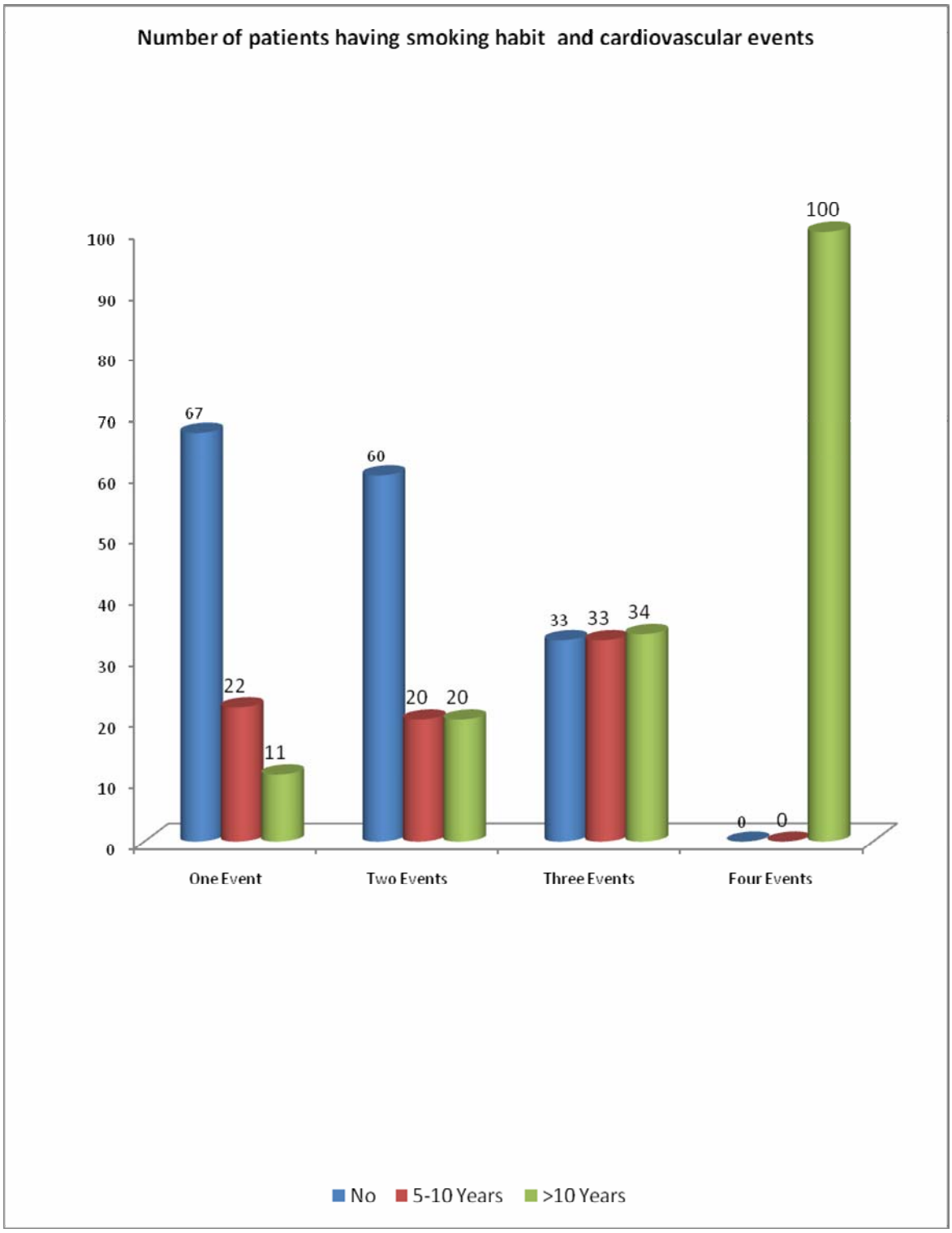
Smoking * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Smoking	No	Count	30	12	1	0	43
		% within Smok	69.8%	27.9%	2.3%	.0%	100.0%
	5-10 year	Count	10	4	1	1	16
		% within Smok	62.5%	25.0%	6.3%	6.3%	100.0%
	>10 years	Count	5	4	1	0	10
		% within Smok	50.0%	40.0%	10.0%	.0%	100.0%
Total		Count	45	20	3	1	69
		% within Smok	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.618[a]	6	.467
Likelihood Ratio	5.085	6	.533
Linear-by-Linear Association	2.373	1	.123
N of Valid Cases	69		

a. 8 cells (66.7%) have expected count less than 5. The minimum expected count is .14.


Number of patients having smoking habit and cardiovascular events
100
90
80
70
60
50
40
30
20
10
0
67
22
11
60
20
20
33
33
34
0
0
100
One Event
Two Events
Three Events
Four Events
No
5-10 Years
>10 Years

Graph No 8

ALCOHOL CONSUMPTION AND CV EVENTS

Table No 9

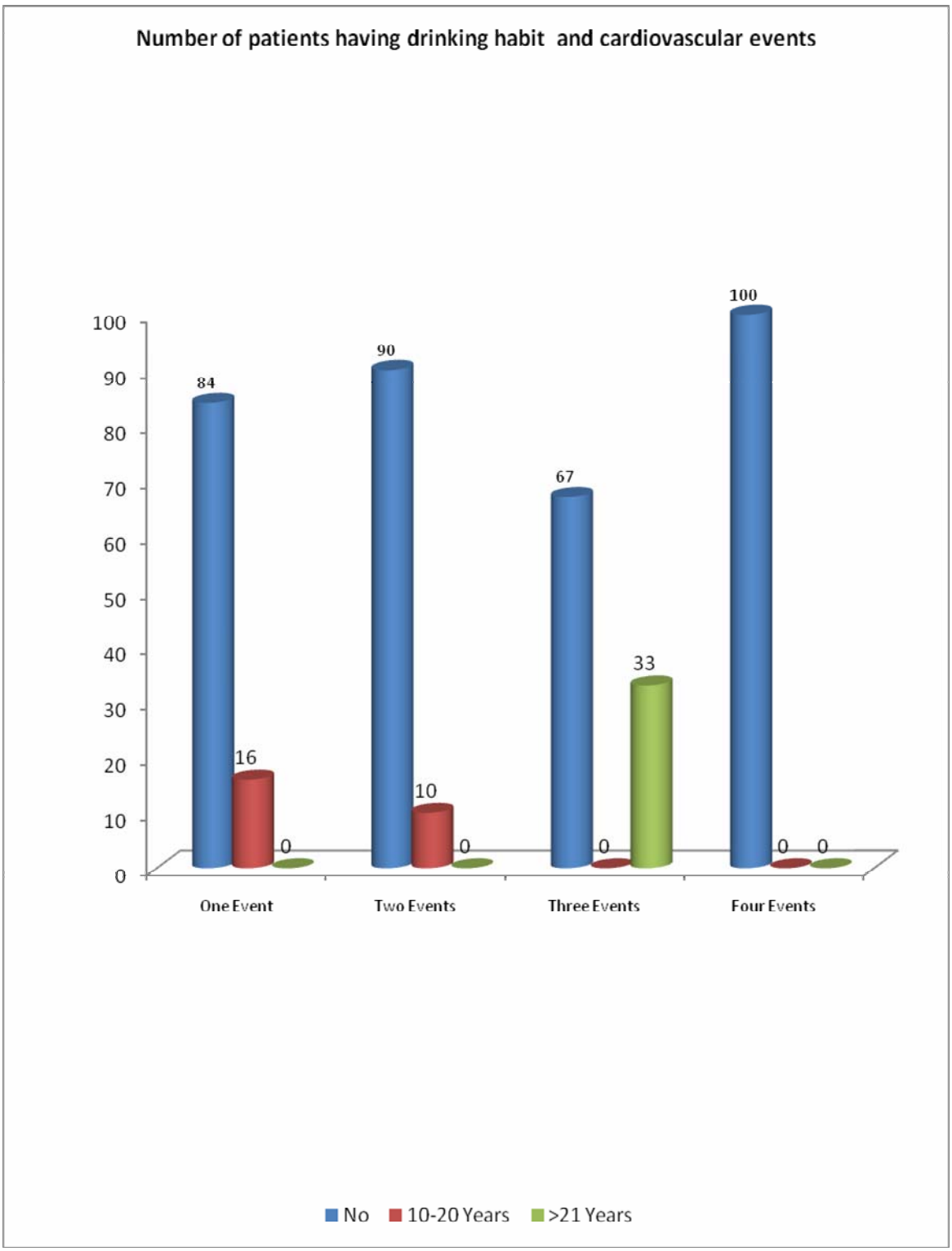
Alcohol * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Alcohol	No	Count	38	18	2	1	59
		% within Alcoh	64.4%	30.5%	3.4%	1.7%	100.0%
	10-20 years	Count	7	2	0	0	9
		% within Alcoh	77.8%	22.2%	.0%	.0%	100.0%
	>21 years	Count	0	0	1	0	1
		% within Alcoh	.0%	.0%	100.0%	.0%	100.0%
Total		Count	45	20	3	1	69
		% within Alcoh	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	23.084[a]	6	.001
Likelihood Ratio	7.884	6	.247
Linear-by-Linear Association	.084	1	.772
N of Valid Cases	69		

a. 9 cells (75.0%) have expected count less than 5. The minimum expected count is .01.


Number of patients having drinking habit and cardiovascular events
100
90
80
70
60
50
40
30
20
10
0
84
16
0
90
10
0
67
0
33
100
0
0
One Event
Two Events
Three Events
Four Events
No
10-20 Years
>21 Years

Graph No 9

BLOOD PRESSURE DISTRIBUTION

Table No 10

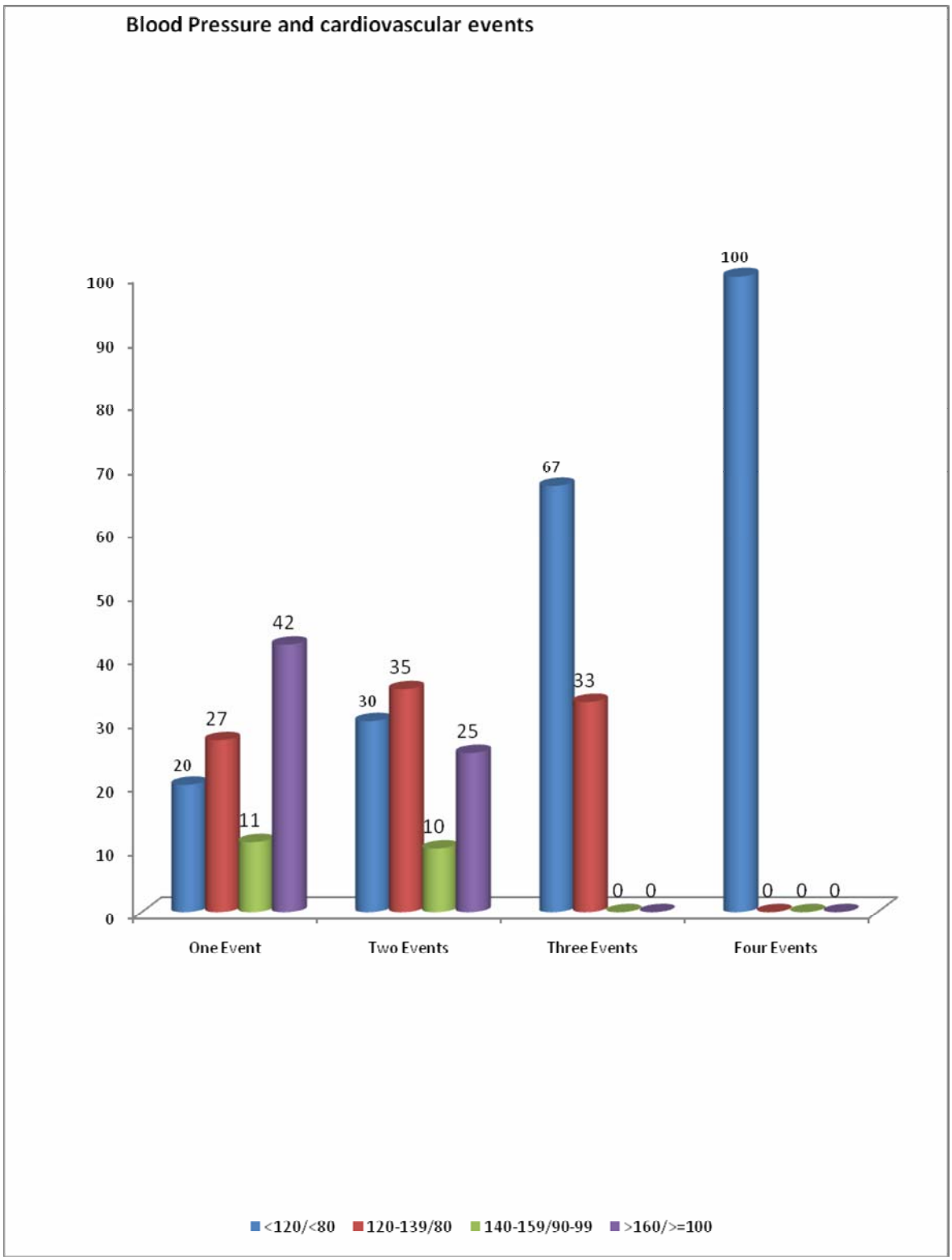
Blood Pressure * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Blood Pressure	<120/<80	Count	9	6	2	1	18
		% within Blood Pressu	50.0%	33.3%	11.1%	5.6%	100.0%
	120-139/80-89	Count	12	7	1	0	20
		% within Blood Pressu	60.0%	35.0%	5.0%	.0%	100.0%
	140-159/90-99	Count	5	2	0	0	7
		% within Blood Pressu	71.4%	28.6%	.0%	.0%	100.0%
	>160/>=100	Count	19	5	0	0	24
		% within Blood Pressu	79.2%	20.8%	.0%	.0%	100.0%
Total		Count	45	20	3	1	69
		% within Blood Pressu	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	8.492[a]	9	.485
Likelihood Ratio	9.168	9	.422
Linear-by-Linear Association	6.391	1	.011
N of Valid Cases	69		

a. 10 cells (62.5%) have expected count less than 5. The minimum expected count is .10.


Blood Pressure and cardiovascular events
100
90
80
70
60
50
40
30
20
10
0
20
27
11
42
30
35
10
25
67
33
0
0
100
0
0
0
One Event
Two Events
Three Events
Four Events
<120/<80
120-139/80
140-159/90-99
>160/>=100

Graph No 10

THYROID STATUS IN CV EVENTS

Table No 11

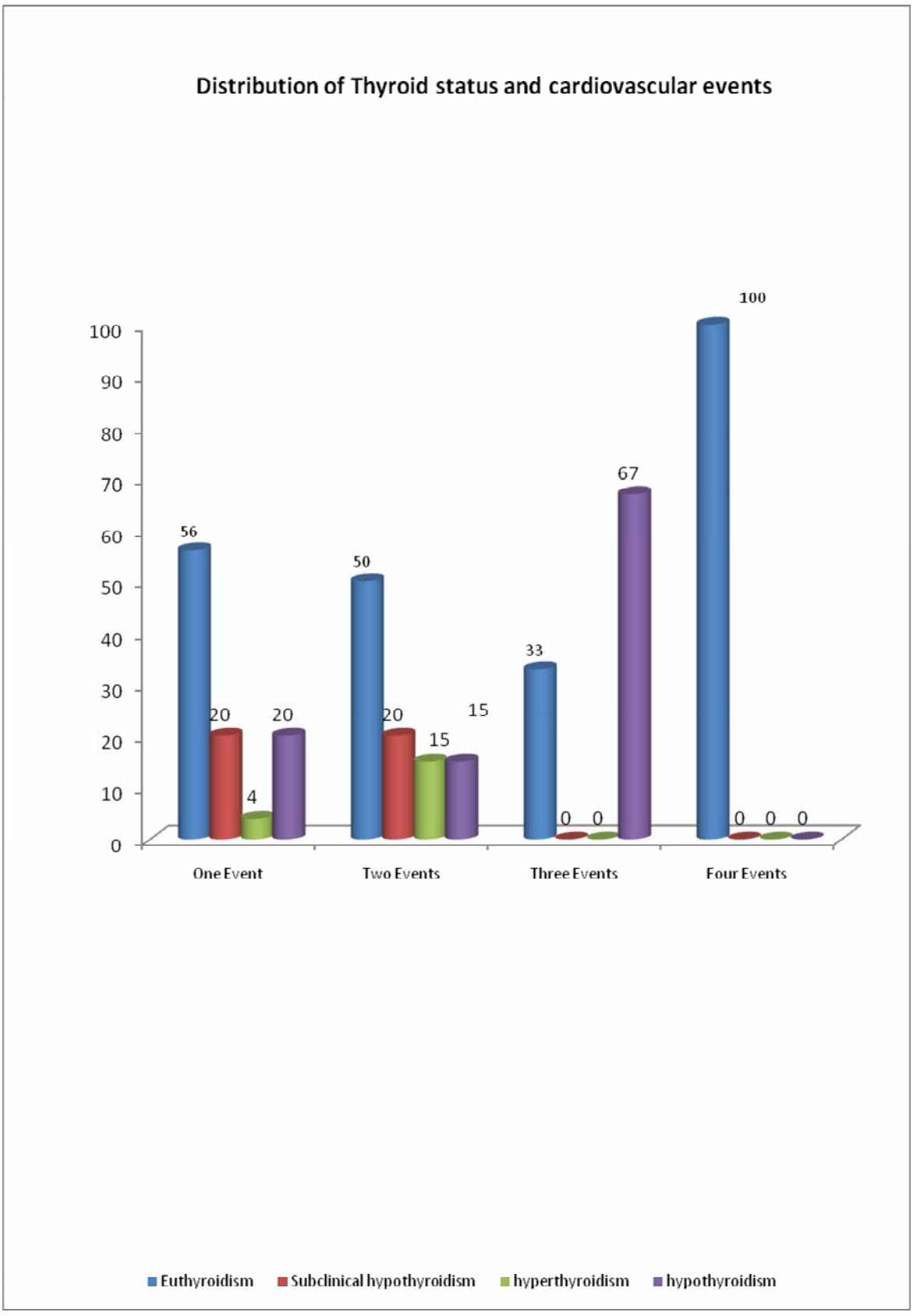
Classification of Thyroidism * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Classification of Thyroidism	Euthyroidism	Count	25	10	1	1	37
		% within Classification of Thyroidism	67.6%	27.0%	2.7%	2.7%	100.0%
	Subclinical Hypothyroidism	Count	9	4	0	0	13
		% within Classification of Thyroidism	69.2%	30.8%	.0%	.0%	100.0%
	Hyperthyroidism	Count	2	3	0	0	5
		% within Classification of Thyroidism	40.0%	60.0%	.0%	.0%	100.0%
	Hypothyroidism	Count	9	3	2	0	14
		% within Classification of Thyroidism	64.3%	21.4%	14.3%	.0%	100.0%
Total		Count	45	20	3	1	69
		% within Classification of Thyroidism	65.2%	29.0%	4.3%	1.4%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	7.609[a]	9	.574
Likelihood Ratio	7.316	9	.604
Linear-by-Linear Association	.426	1	.514
N of Valid Cases	69		

a. 12 cells (75.0%) have expected count less than 5. The minimum expected count is .07.


Distribution of Thyroid status and cardiovascular events
100
90
80
70
60
50
40
30
20
10
0
56
20
4
20
50
20
15
15
33
0
0
67
100
0
0
0
One Event
Two Events
Three Events
Four Events
Euthyroidism
Subclinical hypothyroidism
hyperthyroidism
hypothyroidism

Graph No 11

FINAL STATUS

Table No 12

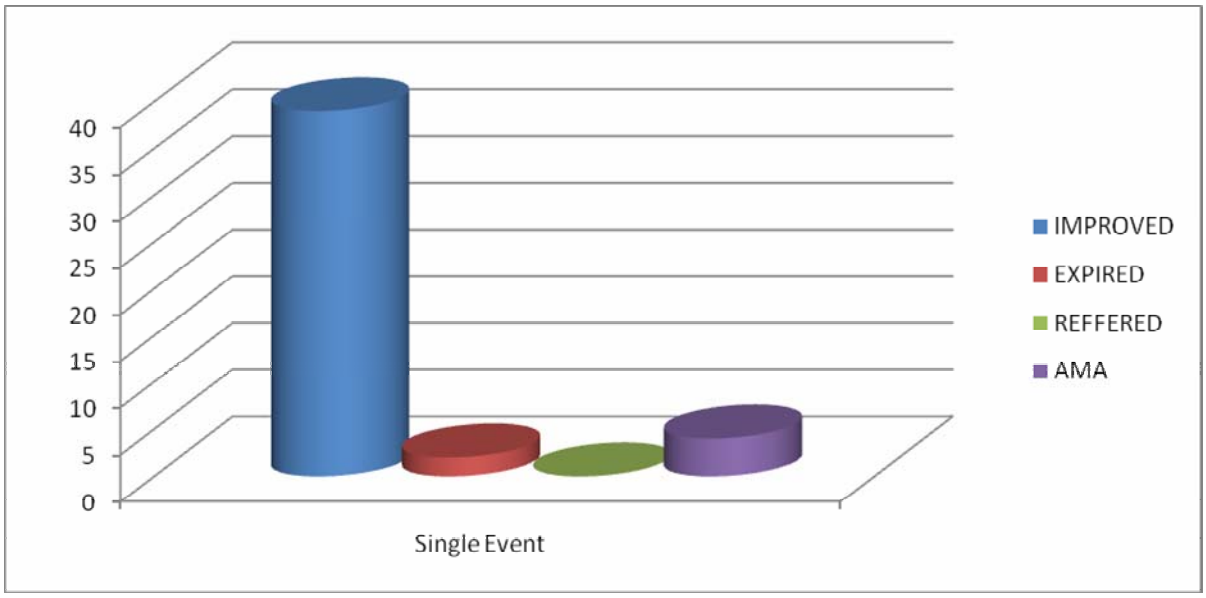
Status * Number of events Crosstabulation

			Number of events				
			One event	Two events	Three events	Four events	Total
Status	AMA	Count	4	0	0	0	4
		% within Stat	100.0%	.0%	.0%	.0%	100.0%
	REFFERE	Count	0	2	1	1	4
		% within Stat	.0%	50.0%	25.0%	25.0%	100.0%
	IMPROVR	Count	39	16	1	0	56
		% within Stat	69.6%	28.6%	1.8%	.0%	100.0%
	EXPIRED	Count	2	2	1	0	5
		% within Stat	40.0%	40.0%	20.0%	.0%	100.0%
Total		Count	45	20	3	1	69
		% within Stat	65.2%	29.0%	4.3%	1.4%	100.0%

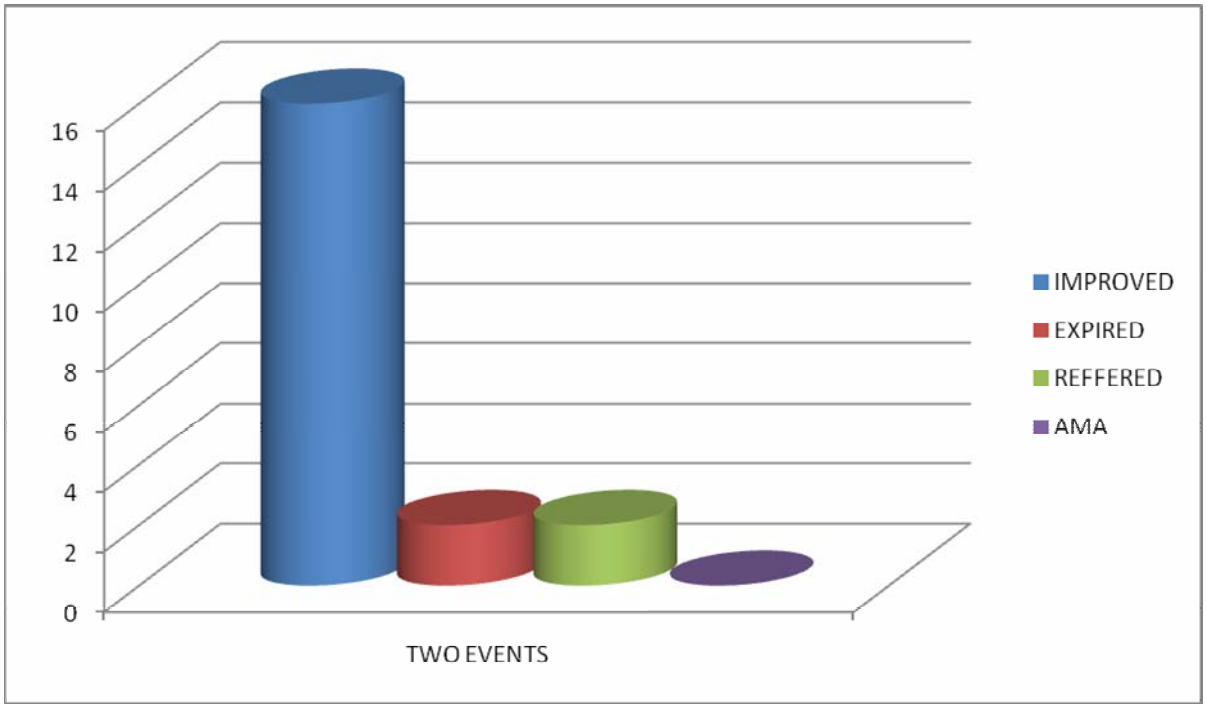
Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	29.999[a]	9	.000
Likelihood Ratio	20.060	9	.018
Linear-by-Linear Association	.000	1	.986
N of Valid Cases	69		

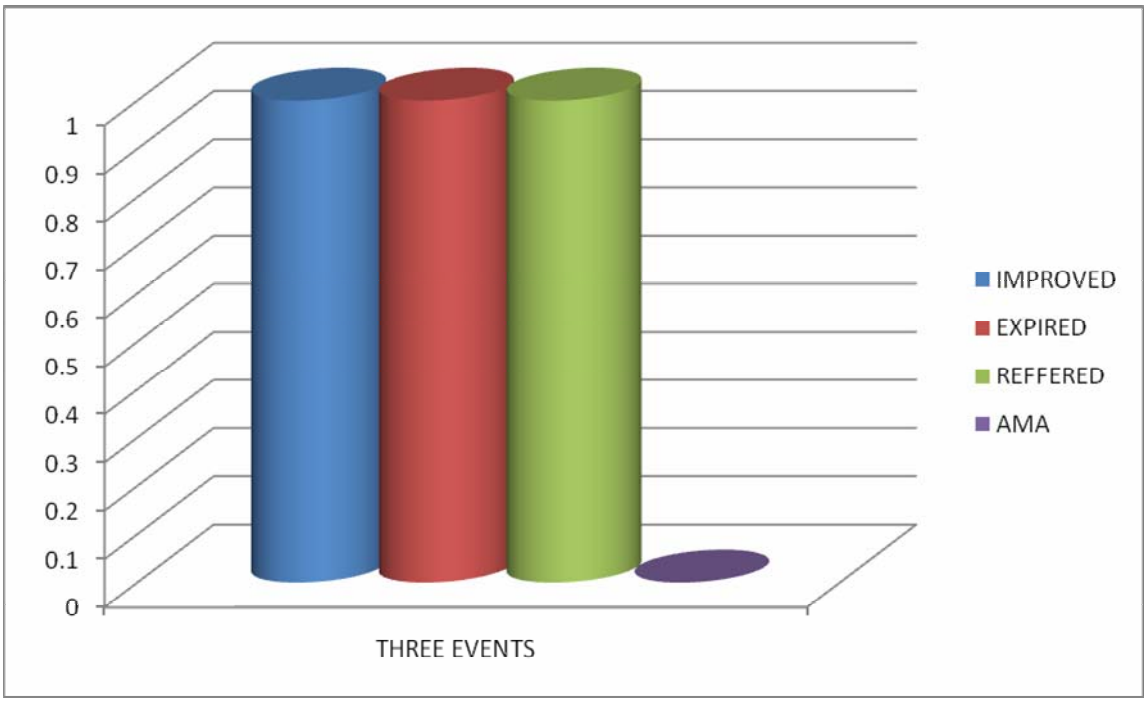
a. 14 cells (87.5%) have expected count less than 5. The minimum expected count is .06.



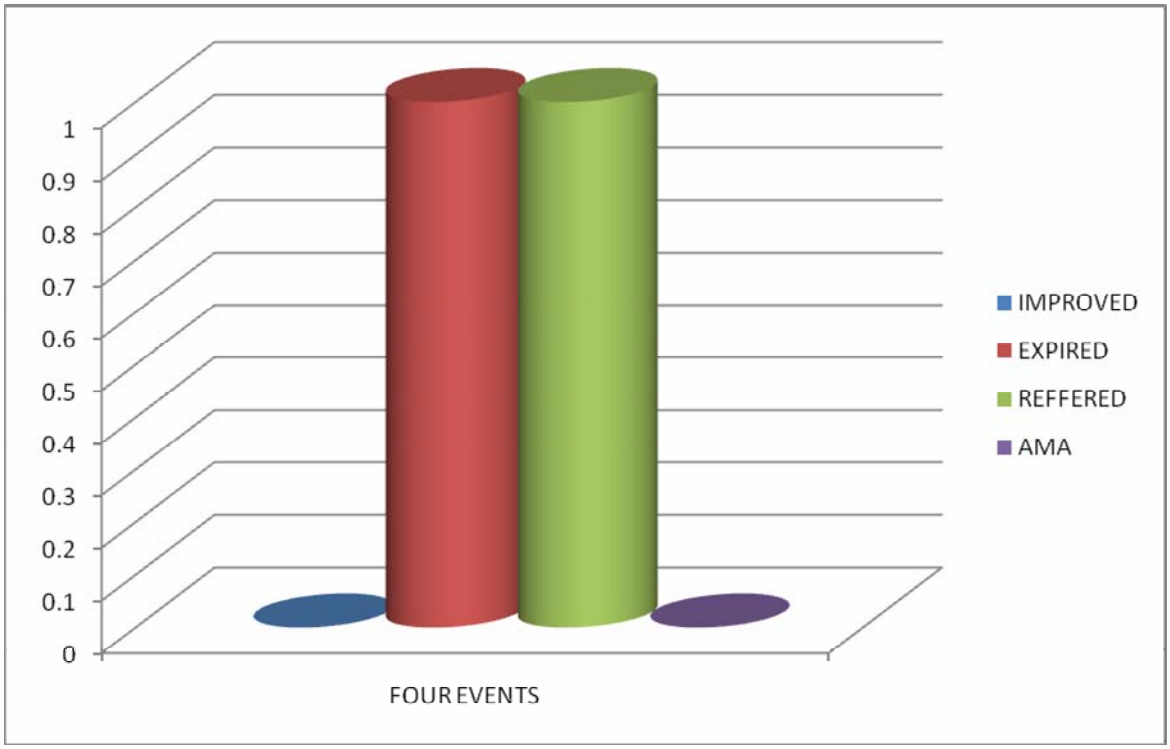
Graph No 12



Graph No 13



Graph No 14



Graph No 15

Statistical Analysis

Study participants' baseline characteristics were summarized according to thyroid status and compared against those in the euthyroid group using a t-test or Chi-Square test as appropriate. Incidence rates of cardiovascular and total mortality and first occurrence of coronary heart disease or cerebrovascular disease were calculated Incidence rates of atrial fibrillation were calculated similarly, excluding only participants with atrial fibrillation at baseline from the risk set. Kaplan-Meier analysis was used to study the cumulative incidence of atrial fibrillation, cerebrovascular disease, coronary heart disease, and mortality by thyroid.

Multivariable Cox regression models were used to estimate the hazard ratio of each thyroid disease group compared to the euthyroid group, adjusting for other baseline risk factors or potential confounders and thyroid medication use during follow-up. Models were originally stratified by CVD status at baseline and by sex. Results were consistent across strata and, when combined, statistical tests for interactions between thyroid group and sex or thyroid group and baseline CVD were not significant. Final models included men and women, and participants with and without CVD at baseline. Models were done in stages, adjusting first for age, sex, disease status at baseline and thyroid medication use during follow-up as a time-dependent covariate. All analyses were done using SPSS for Windows, version 13 and STATA version 9.

DISCUSSION

Thyroid dysfunction is an underrated investigation in our modern medicine, unless warranted. With the growing elderly population and advances in modern medicine and better care and outcome of diseases of the advancing age it becomes even more important to diagnose and predict and treat outcome of all conditions affecting the elderly. Although it has been generally admitted that the prevalence of thyroid dysfunction in the elderly is higher in hospitalized and institutionalized patients than in general population, these findings have not been confirmed in elderly population in our area.[71]

Out of all the elderly patients aged 60 years and above, admitted to B.L.D.E.A's Sri B.M.Patil Medical College, Hospital and Research Center Bijapur, with cardiovascular events from October 2008 to April 2010, 69 random patients were chosen who satisfied all the inclusion criteria.

Out of the 69 patients, there were 43 (62.3%) males and 26 (37.7%) females, with 50 of them between the age of 60-69 (72.5%) years, and 19 (27.5%) of them above 69 years with the eldest at 82 years.

37 (53.6%) of the patients were Euthyroid, while 13 (18.8%) had Subclinical hypothyroidism comparable to 17% and 16.8% levels in study by Singer RB [71] and Gussekloo J[73] , and 14 (20.3%) had hypothyroidism comparable to studies by Colorado , 10% of men and 16% of women age 65-74 had TSH levels that were increased above the upper limit of the reference range, while 16% of men and 21% of women age 75 and older had increased TSH levels[74] , and 5 (7.2%) had hyperthyroidism comparable study by Duarte Glaucia C et all (6.5%)[75].

Females had a higher incidence of cardiovascular events as compared to men 73.1% to 60.5%, but more number of events (two, three and four) was reported higher in male population, which can be attributed to associated factors like smoking and alcohol consumption which were not reported by any female.

45 (65.2%) patients had single cardiovascular events, but 20 (29.0%) and 3 (4.3%) and a single (1.4%) patients also had two, three and four events respectively.

Patients in the age group of 60-69 years had more numbers of events 50, with 32 (64.0%) of them having single event while 14 (28%) had two, and 3 of them had three (6.0%) events while one person had four events. Out of the 19 persons age group of more than 70 years, 13 (68.4%) of them had single event while 6 (31.6%) had two events which are higher as compared to the previous group. Maximum (four) events were seen in a Euthyroid diabetic with history of alcoholism and smoking.

56 (37.95%) of the total patients improved and were discharged from this hospital, while five (3.45%) of them expired and four each were either referred to higher center or were discharged against medical advice.

Out of the five whom expired four of them had history of hypertension out of which three of them had Cerebrovascular events (two had infarct stroke and one Intracerebral hemorrhage), three of them also had concomitant Diabetes mellitus. Of the four patients who were referred to higher center all had more than single event, two with two events each and one each with three and four events. Two had developed arrhythmias, while one had developed cardiomyopathy. Two each had concomitant diabetes and had developed pleural effusion.

The ageing process is often accompanied by a decrease in the concentration of T3 because of a reduction in the activity of peripheral desiodase. The most common

disorder is the reduction of FT3 (low T3 syndrome), whereas the reduction of FT4 is uncommon and TSH concentrations have been found normal, high or low. Other factors such as acute and chronic nonthyroidal illness and several drugs may be accompanied by changes in thyroid function tests.[76 77 78]

Several authors have investigated the relationship between thyroid function and morbidity and mortality in elderly population. Some studies conducted to date, although not all, suggest that decreased TSH and increased FT4 levels are associated with an increase in mortality, whereas a mild thyroid hypofunction seems to behave as a factor that increase survival in elderly[73 79 80]

A correlation of low T3 concentrations with the severity of illness in elderly hospitalized patients has been reported [81] A recent study of 282 elderly hospitalized geriatric women showed that low T3 syndrome was strongly associated with a high Prognostic Nutritional Index, low Mini Mental State Examination (MMSE) score, and with adverse outcome (institutionalization and death during hospitalization) [82] Women with intermediate or high levels of thyrotropin (1.14 - 2.52 mIU/L and 2.5 - 3.5 mIU/L, respectively) had hazard ratios for CHD death of 1.41 and 1.69 compared with women who had levels of thyrotropin in the lower range of normal (0.50 - 1.4 mIU/L). This trend was statistically significant in women ($p = 0.005$) but not in men.[83]

Compared with euthyroid participants, CHF events occurred more frequently among those with a TSH level of 7.0 mIU/L or greater (35.0 vs. 16.5 per 1000 person-years; $P = .006$), but not among those with TSH levels between 4.5 and 6.9 mIU/L. In multivariate analyses, the risk of CHF was higher among those with high TSH levels (TSH of 7.0-9.9 mIU/L: hazard ratio, 2.58; and TSH of ≥10.0 mIU/L: hazard ratio,

3.26). Among the 2555 participants without CHF at baseline, the hazard ratio for incident CHF events was 2.33 in those with a TSH of 7.0 mIU/L or greater.[84]

An Australian study of over 2,000 subjects (mean age 50 years, age range 17-89 years) found 5.6% to have subclinical hypothyroidism. Over a 20-year period those with subclinical hypothyroidism having plasma TSH greater than 10 μIU/mL were more than twice as likely to have a coronary heart disease event (fatal or nonfatal) as normals. Those with subclinical hypothyroidism having plasma TSH less than 10 μIU/mL were more than one-and-a-half times as likely to have a coronary heart disease event as those with normal TSH. [85]

22 (31.9%) patients had prior history of hypertension on admission, with 10 (14.5%) of them of less than 5 years history and 11 (15.9%) of them had for 5-10 years and 1 (1.4%) had for more than 10 years.

54 of the patients did not have diabetes on presentation, and of the 15 who had, 6 (8.7%) had for less than 5 years, while 7 (10.1%) had for 5 - 10 years, while 2 (2.9) had for more than 10 years.

43 (62.3%) had no history of smoking, while 16 (23.2%) had less than 5 pack years history, while 16 (23.2%) had 5 – 10 pack year history and 10 (14.5%) more than 10 pack year history. 59 (85.5%) had no history of alcohol consumption, 9 (13.0%) had been consuming for less than 20 years; and 1 (1.4%) patient had consumed it for more than 20 years.

SUMMARY

Although out of the 69 patients randomly chosen 53.6% were Euthyroid, 46.4% had one or the other thyroid dysfunction comparable with numerous other studies.

Most common being hypothyroidism 39.1% (18.8% being subclinical and 20.3 % frank hypothyroidism).

Although females represented only 37.7% of the patients they had more incidences of events as compared to the men 73.1% to 60.5%. Whereas more number of events (two or more) was seen in the male population,

65.2% of patients had single cardiovascular event, while 29% had two events, and rest more than two events.

Patients in the 70 and above age group had higher incidences rate of events.

Patients who either expired or were referred to higher centers had two or more events with underlying other chronic medical conditions.

CONCLUSION

In this study, I have concluded that Thyroid profiling can be used as a bio-marker in the elderly population to ascertain cardiovascular risk.

Hence, identifying person at risk of developing cardiovascular complications in the future by thyroid profiling, thus modifying the disease process and preventing morbidity and mortality.

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ANNEXURE

CASE PROFORMA

B.L.D.E.A'S SHRI. B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, BIJAPUR

THYROID DYSFUNCTION AS COMORBID CONDITION IN CARDIOVASCULAR EVENT IN ELDERLY PATIENT

PROFORMA

Name: **IP. No:**

Age: **Address:**

Sex: **Date of Admission:**

Occupation: **Date of Discharge:**

Religion: **Status at Discharge:**

Provisional Diagnosis

Final Diagnosis

Result

PRESENTING COMPLAINTS:

Chest pain- Yes/No

Onset

Duration

Type

Site

Radiation

Aggravating factors

Relieving factors

Associated symptoms

Palpitation- Yes/No

Onset

Duration

Type

Aggravating factors

Relieving factors

Associated symptoms

Breathlessness-

Onset

Duration

Type Exertional/ Episodic

Grade

Wheeze

Aggravating factor

Relieving factor

H/o Orthopnoea

H/o P.N.D

Swelling of lower limbs Yes/No

Onset

Duration

Progress

Diurnal variation

Puffiness of face- Yes/No

Onset

Duration

Progress

PAST HISTORY:

History of hypertension

Duration

Treatment history

History suggestive of MI/ Angina

History suggestive of DM

History suggestive of R.H.D

H/o Drug intake

Steroid/ Aminodrone/ Any thyroid medication

FAMILY HISTORY:

History suggestive of Ischemic Heart Disease/ Hypertension/ Diabetics

PERSONAL HISTORY:

Diet/Appetite

Sleep

Bladder and bowel habits:

Smoking /Tobacco chewing/Snuff Inhalation

Duration

Number of cigarettes / beedis pack year smoked

Amount of tobacco chewed/ snuff inhaled

Alcohol

Duration

Quantity/Frequency

Type

GENERAL PHYSICAL EXAMINATION:

Pallor:

Icterus:

Cyanosis:

Clubbing:

Pedal edema:

Lymphadenopathy:

B.M.I.

Hypothyroidism facies:

Vital Signs:

Pulse rate:

Blood pressure:

Temperature:

Respiratory rate:

Signs of Thyroid Dysfunction

Goitre

Hoarseness

Xanthelasma

Delayed relaxation of tendon reflex/ Hyper-reflexia, Ill-sustained clonus

Carpal tunnel syndrome

Cerebellar ataxia

Myotonia

Dry, flaky skin and malar flush

Carotenemia

Alopecia, Vitiligo

Myxodema

Constipation, IIeus, Diarrhoea,

Ascites

Weight loss, Anorexia

Palpitation

Ankle odema

Tremor

Increased sweating

Palmer erythema, spider naevi

Occular signs:

Lid retraction/lid lag

Exopthalmos/ Exposer keratitis/ Corneal Ulceration

Ophthalmoplegia/ Diplopia

Gynaecomastia

CARDIOVASCULAR SYSTEM:

Peripheral

Arterial Pulse

Rate

Rhythm

Volume

Character

Symmetry

Radio-radial

Radio-femoral

Pulse deficit

Other Peripheral Pulses	Rt	Lt
Radial		
Brachial		
Carotid		
Femoral		
Poplitial		
Posterior Tibila		
Dorsalis pedis		

Blood Pressure Rt.
Lt.

Upper Limb

Lower Limb

Signs of Congestive Cardiac Failure

Exaggerated hepato-jugular reflex

Raised Jugular Venous pressure

Wave form

Tender hepatomegaly

Pitting pedal odema

Miscellaneous

Clubbing

Cyanosis

Central

Inspection

- Precordial bulge

-Apical impulse

-Other pulsations

Suprasternal pulsation

Supraclavicular pulation

Right and left 2nd intercostals spaces

Parasternal pulsation

Epigastric pulsation

Palpation

Apical impulse

Site

Character

Parasternal palpation

Haeve

Diastolic thud (palpable P2)

Thrill

- Mitral area
- Tricuspid area
- Pulmonary area
- Aortic area

Percussion

- Cardiac border
- Left and right 2nd intercostals space
- Lower sternum
- Upper border of liver

Auscultation

- **Heart sound**
  - Mitral area
  - Tricuspid area
  - Pulmonary area
  - Aortic area
- Murmur
  - Mitral area
  - Tricuspid area
  - Pulmonary area
  - Aortic area
- Added sounds
  - Clicks
  - Opening snap

Pericardial rub

RESPIRATORY SYSTEM:

GASTROINTESTINAL SYSTEM

CENTRAL NERVOUS SYSTEM:

PROVISIONAL DIAGNOSIS:

INVESTIGATIONS

I.HAEMATOLOGY

Haemoglobin	**gm/dl**
TC	**Cells/mm^3**
DC	
Neutrophils	**%**
Lymphocytes	**%**
Eosinophils	**%**
Basophils	**%**
Monocytes	**%**
ESR	**mm/1hr**

II.URINE

Albumin	
Sugar	
Microscopy	

III.BIOCHEMISTRY

RBS **mg/dl**

FBS **mg/dl**

PPBS **mg/dl**

mg/dl

S.creatine

CPK MB
LIPID

Cholesterol

Triglyceride

LDL

VLDL

HDL

IV. THYROID LEVELS

TSH	µU/ml
T3	ng/ml
T4	µg/dl

V. ECG

VI. ECHO

VII. COLOUR DOPPLER AND TRESDMILL STRESS TEST

VIII. FINAL DIAGNOSIS

IX. RESULT

SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTER,

BIJAPUR – 586103.

CONSENT FORM

TITLE OF RESEARCH : THYROID DYSFUNCTION AS CO-MORBID CONDITION IN CARDIOVASCULAR EVENTS IN ELDERLY PATIENT

GUIDE : Dr. R.C.Bidri

P.G. STUDENT : Dr. Abhishek Gaurav

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to evaluate THYROID DYSFUNCTION AS CO-MORBID CONDITION IN CARDIOVASCULAR EVENTS **IN** ELDERLY PATIENT

PATIENT PROCEDURE:

I understand that I will undergo detailed history and clinical examination after which blood will be collected & sent to the laboratory for investigations.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved and I may experience mild pain during the collection of blood.

BENEFITS:

I understand that my participation in this study will help in recognition of existence of HYPOTHYROISM AS COMORBID CONDITION IN CARDIOVASCULAR EVENT IN ELDERLY PATIENT.

CONFIDENTIALITY*:*

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulations of hospital. If the data is used for publications, the identity of the patient will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw for study at any time.

INJURY STATEMENT:

I understand in the unlikely event of injury to me during the study I will get medical treatment but no further compensations.

(Signature of Guardian) (Signature of patient)

(If the patient is conscious, well oriented and fully aware)

KEY TO MASTER CHART

- In Patient Number IP No.

Sex

- Male M
- Female F

Cardiovascular Events

- Arrythmias 1
- Congestive Heart Failure 2
- Myocarditis 3
- Coronary Artery Disease 4
- Cardiomyopathy 5
- Diastolic Dysfunction 6
- Hypertension 7

Comorbid Conditions

- Diabetes Mellitus DM
- Chronic Obstructive Pulmonary Disease COPD
- Cerebrovascular Accident Stroke
- Hypertriglyceridemia Hypertrygly
- Ishemic Heart Disease IHD
- Hypertension HTN
- Intra cranial Bleed IC Bleed
- Urinary Tract Infection UTI

Thyroxine T4

Triiodothyronine T3

Thyroid Stimulating hormone THS

RBS	Random Blood Sugar
CPKMB	Creatine Phosphokinase MB
AMA	Discharged Against Medical Advice

Name	Age	Sex	IP No.	Cardiovascular Event	Asso. Finding	H/o HTN No.Yr	H/o DM no Yr	Smoking (Pack Yr)	Alcohol/Yr	BMI	Pulse	BP	TSH	T3	T4	CPKMB	RBS	ECG Changes	ECHO Changes	IMPROVED/EXPIERD
Bassappa Chalwadi	65	M	10114	7	COPD	NO	NO	15	NO	20.1	82	150/100	5.7	1.6	9.8		225	YES	NO	IMPROVED
IRRAPPA GUDADINI	60	M	10100	4+7	HTN	NO	NO	NO	NO	28.6	76	170/100	7.8	0.4	2.9	23	108	YES	YES	IMPROVED
SANGAPPA	60	M	9394	7	COPD	NO	NO	20	NO	19.6	84	160/94	3.8	1.6	6.2		94	NO	NO	IMPROVED
N K MASGI	69	M	9793	7	DM	0.5	20	30	NO	19.6	76	158/94	0.9	1	3.2		211	NO	NO	IMPROVED
ANNAPPA SHINDE	72	M	9824	7	COPD	NO	NO	25	NO	18.6	100	156/92	5.4	1.6	8.9		97	YES	NO	IMPROVED
MAHADEVI	68	F	9994	7	Puneumonia	NO	NO	NO	NO	24.1	106	150/90	4	1.4	6.8		98	NO	NO	IMPROVED
GANGAWWA	75	F	9964	7	IC BLEED	1	1	NO	NO	18.6	80	160/80	4.8	0.8	5.3		126	YES		EXPIRED
SUSHILABAI	65	F	7436	4		NO	NO	NO	NO	28.4	108	140/80	0.03	15	1.9	39	150	YES	YES	IMPROVED
MAHABUBLE QURESHI	63	F	6703	7	TIA+DM	10	10	NO	NO	30.6	86	180/90	0.8	1.8	10.4		198	YES	NO	IMPROVED
IRAYYA GOBIMATH	63	M	9954	7	DM+UTI	NO	NO	NO	NO	20.4	84	164/90	3.4	1.2	7.3		192	NO	NO	IMPROVED
LAKKAPA	65	M	9876	1		NO	NO	NO	NO	24.6	239	160(SYS)	0.6	1.9	15	29	121	YES	NO	IMPROVED
SHARANGOUDA	65	M	18672	4+2+1	PLU EFFUSION	NO	NO	30	30	19.7	50	120/70	4.3	0.24	3.1	38	112	YES	YE	REFFERED

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SULOCHANA	69	F	1029	7+4		8	NO	NO	NO	30.6	68	130/80	0.01	3.36	1.96	49	113	YES	NO	IMPROVED
VISHWANATH KINAGI	72	M	20049	7+4	DM+BBPV	4	2	12	12	26.8	70	140/98	0.8	1.6	10.4	32	136	YES	NO	IMPROVED
BASSAPPA BANIKER	65	M	19851	4	COPD	NO	NO	27	15	26.4	86	136/78	2.8	1	3.8	87	145	YES	YES	IMPROVED
HANAMANTRAO JOSHI	82	M	20258	7	STROKE	NO	NO	NO	NO	26.4	88	220/90	0.6	1.8	9.6	48	138	NO	NO	EXPIRED
SUMITRA MORE	78	F	1830	4+7	DM	6	5	NO	NO	16.7	118	200/70	4.1	1.16	8.4	60	221	NO	NO	IMPROVED
GIRAMALLAPPA	67	M	1596	7	TIA	3	NO	NO	NO	34.6	74	160/90	4.8	0.9	8.1		88	NO	NO	IMPROVED
SHIVAMMA KOTENAVARN	75	F	19197	7	STROKE	NO	NO	NO	NO	NA	80	200/70	1.4	1.4	10.4		156	NO	NO	AMA
BASAPPA WAGANGLE	65	M	18738	7+4+2+1	DM	14	14	10	NO	41.7	100	118/60	0.8	10.6	1.6	87	137	YES	YES	REFFERED
SATTAPA DUDAWAR	62	M	9116	7+4		NO	NO	30	NO	26.4	86	184/96	4.3	1.2	8.4	107	146	YES	YES	IMPROVED
SOMANGOUDA	65	M	1762	7+4	DM	NO	NO	NO	NO	42.1	78	160/100	0.3	3.6	13.4	237	228	YES	YES	IMPROVED
SHANKERAPPA	60	M	19020	7	OLD IHD	2	NO	15	12	38.2	76	186/94	4.3	0.9	8.7	28	115	YES	YES	IMPROVED
PARVATI TANGADI	64	F	20036	7	DM	5	5	NO	NO	28.7	88	170/90	0.3	3.6	14.8	36	297	YES	YES	IMPROVED
RANAGONDA PUJARI	72	M	1821	4	HYPER TRYGLY	NO	NO	17	20	40.6	58	136/84	4.6	1.6	8.4	96	84	YES	YES	IMPROVED
RAJGOPAL SHAPU	70	M	767	7+4	DM+ARF+ANEMIA	4	8	NO	NO	26.2	80	114/80	3	0.9	6.8	36	136	YES	YES	EXPIRED

SHIVALINGAMMA	80	F	14829	7+4	DM+STROKE	7	4	NO	NO	23.6	78	164/88	1.9	1.4	15		135	YES	YES	EXPIRED
BASAYYA HIREMAT	68	M	228	7+4		NO	NO	25	20	36.66	60	146/90	5	6.12	1.6	19	98	YES	YES	IMPROVED
RAUGU CHAWAN	68	M	8757	4	COPD	NO	NO	25	20	26.7	90	140/80	0.6	1.6	10.4	87	128	YES	YES	IMPROVED
ANANTRAO YADAWAD	67	M	19511	7	EPISTAXIX	2	NO	NO	NO	40.6	72	180/100	4.3	0.7	6.3	42	94	YES	NO	IMPROVED
KASHINATH	61	M	10760	4+2		NO	NO	NO	NO	28.7	84	126/68	4.7	1.3	7.9	64	100	YES	YES	IMPROVED
SHANTAWA	63	F	2490	4+2+6		NO	NO	NO	NO	26.8	82	116/56	3.1	1.2	8.9	102	88	YES	YES	IMPROVED
BHIRAPPA	69	M	2427	7+5	PUL EFFUSION	3	NO	16	NO	31.6	108	100/62	0.8	2.2	11.8	58	112	YES	YES	REFFERED
SANGAMMA	76	F	3054	1		NO	NO	NO	NO	27.4	46	122/74	5.8	1.6	8.5	29	67	YES	NO	IMPROVED
SANGAPA	60	M	2798	4+6	COPD	NO	NO	22	NO	25.8	78	106/68	3.7	0.9	7.3	107	89	YES	YES	IMPROVED
SHANTAMMA	73	F	2134	7	DM	NO	NO	NO	NO	25.5	78	156/100	2.7	0.9	5.2		108	YES	NO	IMPROVED
SHREEDEVI	66	F	7633	1		NO	NO	NO	NO	27.6	164	130/88	4.5	1.4	8.4	75	93	YES	NO	IMPROVED
MUYYAYYA	62	M	7981	4		NO	NO	17	NO	28.3	86	114/70	3.7	1.4	7.1	92	103	YES	YES	IMPROVED
SHAVITHA	70	F	11039	7	STROKE	NO	NO	NO	NO	26.5	74	220/106	2.7	1.3	4.9		112	YES	NO	AMA
VIJAYLAKSHMI	64	F	10596	4+2		NO	NO	NO	NO	33.1	84	104/74	4	0.9	3.6	103	84	YES	YES	IMPROVED
SUSILABAI	67	F	11045	7	STROKE	6	NO	NO	NO	25.8	70	184/102	1.2	1.6	11.5		78	YES		IMPROVE

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MOHNEESH	66	M	10419	4	DM	NO	3	NO	NO	32.8	68	118/82	5.8	0.7	4	78	100	YES	YES	IMPROVED
SHANTTAPPA BIRADAR	63	M	9542	7+4		NO	NO	NO	NO	27.4	68	108/60	4.8	1.1	7.9	62	87	YES	YES	IMPROVED
SHIV KUMAR	70	M	372	2	OLD IHD	NO	NO	NO	NO	23.6	88	106/60	3.3	0.9	6.5	47	72	YES	YES	IMPROVED
RAVATTAPP G H	64	M	4871	7	HYPER TRYGLY	NO	NO	NO	NO	42.7	70	110/64	3.6	1.4	9.2		82	NO	NO	IMPROVED
SHIVAKUMAR	68	M	4012	4+2+1	DM	NO	6	15	NO	31.7	68	94/50	4	1.1	4.3	67	94	YES	YES	EXPIERED
SIDDAPA HANAGJI	76	M	5732	7	STROKE	5	NO	17	NO	27.6	112	178/96	3.8	1.5	5.9		102	YES		AMA
SANGAPPA JOSHI	64	M	9120	4	HEART BLOCK	NO	NO	19	NO	28.5	58	116/68	2.4	1.4	6	80	78	YES	YES	IMPROVED
BANDU	63	F	13053	7	STROKE	8	NO	NO	NO	22.6	68	200/90	1.8	1.2	7.5		69	NO	NO	IMPROVED
SUMANGALA	76	F	2074	7+5		5	NO	NO	NO	25.4	68	130/72	4.7	0.7	5.3		83	NO	YES	IMPROVED
HAYYASIDDA H KORI	60	M	10074	4	DM	NO	3	12	10	26.5	82	114/68	7.9	0.2	3.6	65	106	YES	YES	IMPROVED
PARVATI	70	F	14367	4	HYPER TRYGLY	NO	NO	NO	NO	38.4	74	118/80	3.8	1.2	8.3	54	87	YES	YES	IMPROVED
HASHIMPEER RAO	66	M	7312	4+6		NO	NO	25	NO	26.7	92	120/68	4.2	1	7.4	105	96	YES	YES	IMPROVED
PARSAPPA METI	67	M	200137	7	STROKE	10	8	17	15	NA	112	192/102	9.6	0.1	1.3		121	NO	NO	AMA
RENUKA AGGARWAL	60	F	6830	4		NO	NO	NO	NO	33.5	68	110/64	4.1	1.4	5.9	34	89	NO	NO	IMPROVED
SUJATHA MANDAR	61	F	7301	4		NO	NO	NO	NO	31.6	82	122/68	3.6	1.2	8.2	79	72	YES	YE	IMPROVE

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MD ALLARAKHA	67	M	4814	7+4	DM	8	3	NO	NO	38.7	80	132/80	4	1.6	7.3	56	67	YES	YES	REFFERED
SHOBHA DEVI	62	F	11023	7+6		NO	NO	NO	NO	23.8	90	114/72	5	1.1	4.8		92	NO	YES	IMPROVED
VIDYASHREE	66	F	6367	4	HYPER TRYGLY	NO	NO	NO	NO	32.7	76	102/62	4.6	1.3	7.1	71	112	YES	YES	IMPROVED
RAVI YELLARKI	65	M	5102	7	DM	NO	NO	NO	NO	27.1	78	116/84	2.7	1.4	5.9		241	NO	NO	IMPROVED
IRANNA MAHTO	70	M	16045	7+4	COPD	NO	NO	17	NO	23.8	86	126/78	5	1.5	7.2	67	90	YES	YES	IMPROVED
PUDKI	66	M	10023	2	OLD IHD + DM	NO	5	NO	NO	25.6	68	100/50	3.5	1.6	7.3	43	178	YES	YES	IMPROVED
SHILA PATIL	64	F	832	4		NO	NO	NO	NO	28.3	72	116/78	4.7	1.1	8.5	60	90	YES	YES	IMPROVED
MD AJMAL	73	M	2071	4		NO	NO	NO	NO	37.2	80	124/68	6.1	0.8	4.2	77	78	YES	YES	IMPROVED
SHARNAPPA PATIL	68	M	20172	7		3	NO	21	NO	32.7	76	178/90	3.9	0.9	4.7		84	NO	NO	IMPROVED
SEEMA ISSAC	67	F	4471	4		NO	NO	NO	NO	28.3	74	116/82	4	1.4	6.7	76	80	YES	YES	IMPROVED
MD ISHTIYAQ	62	M	14823	7+4	HYPER TRYGLY	3	NO	10	NO	34.7	68	120/62	9	0.03	1	71	78	YES	YES	IMPROVED
IRAMMA MATHEW	76	M	2087	1		NO	NO	20	20	29.5	136	136/80	4.8	1.4	6.1	40	77	YES	YES	IMPROVED
REKHA	60	F	11072	4+2		NO	NO	NO	NO	26.O	102	104/52	3.9	1.3	5.7	58	102	YES	YES	IMPROVED