

Use Of Ace Inhibitors Or ARA II As Nephroprotection In Normotensive Normoalbuminuria Diabetic Patients

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ABSTRACT

The prevalence of diabetes mellitus (DM) is increasing throughout the world quickly driven by the increase of obesity, hyperglycemia due to the resistance to insulin, lipid accumulation renal, inflammation and activation of the renin-angiotensin system (RAAS), which contributes to the development of microvascular and macrovascular complications, as in the pathogenesis of diabetic nephropathy (ND). The adipose tissue is a key organ in the resistance to the insulin; the adipocytes are the origin of an inflammatory process that is characterized by the infiltration of macrophages and increase of inflammatory cytokines, which leads to the initiation of the diabetic nephropathy. The RAAS is closely associated with the generation of reactive oxygen species (ROS) in the diabetic nephropathy; whereas hyperglycemia prolonged produces mitochondrial ROS, which leads to the microvascular complications of diabetes. **Objective:** of this retrospective study is to assess the effect of IECAS or ARA II in patients with DMII normoalbuminuria, normotensive as renoprotective and to prevent future complications irreversible, as its evolution in the diabetic nephropathy and hypertension. **Methods and Analysis:** This study was conducted with 116 patients within the ages of 20 - 70 years of age having DM II from 2002 until the present normotensive and normoalbuminuria of which 64 are men and 52 women with multiple risk factors such as obesity, overweight diseases history family coronary, smoking and sedentary mostly, 91 patients receive Lisinopril (ACEI) 5mg and 25 patients losartan (ARAI) 25mg per night continuously from the time DM II is detected. **Results:** The prevention of microalbuminuria, despite its limitations, is clinically important in the attention of our cases as a noble proposal, practical, achievable, of low cost and with extraordinary results in primary prevention in the present and future of the patients with DM II. In addition because the IECAS AND ARAII are used when the patient presents an irreversible damage with an uncertain future. **Conclusions:** I share my experience of more than 14 years using low doses of lisinopril 5mg or Losartan 25mg ingested by the nights continuously in patients present with DMII normoalbuminuric of several years of evolution of their disease without hypertension. Possibly a study or investigation with many defects but with undeniable beneficial, even more in our country Ecuador that has epidemiological characteristics similar to many countries of the world, and where the dialysis units are not supplied to give palliative treatment for diabetic patients with CRF, causing exorbitant costs of millions of dollars in this chronic disease that is not transmittable. I would venture to say that, Doctors should begin to use in all diabetic cases the drugs listed above for a long time and continuous monitoring of the patient.

Keywords: Diabetes mellitus, endothelial dysfunction, hyperglycemia, oxidative stress, inflammation, renin angiotensin aldosterone (RAAS), normoalbuminuric .

Introduction

The diabetes mellitus type 2 (DMII) has become one of the public health problems more challenging around the world, which affects approximately 410 million people and that represent 1.3 million deaths in 2013, the double that of 1990 and affected patients highlight a greater risk of the harmful effects of hyperglycemia as the coronary artery disease, peripheral arterial, and ultimately the strokes. Prolonged hyperglycemia can lead to development of complications such as vascular micro diabetic nephropathy, retinopathy and neuropathy. The number of people with diabetes is growing and the figure is expected to reach 552 million in 2030, due to many factors such as population growth, aging, urbanization, obesity and physical inactivity (Catalá-López *et al.*, 2016).

Medicines intended for the inhibition of the renin-angiotensin system (SRA) have been extensively used for the prevention of renal and cardiovascular events in patients with Diabetes. The blockade of the RAAS is a therapeutic target key because it controls the volume balance and electrolyte circulation and is an important regulator of the hemodynamic stability. At present, three classes of medications that interact with the SRAA is used to inhibit the effects of angiotensin II: inhibitors of the angiotensin-converting enzyme (ACE), angiotensin receptor blockers (ARBS), and the direct inhibitors of renin (DR) (Tikellis *et al.*, 2014).

Most of the evidence-based guidelines for the management of hypertension and diabetes have generally recommended the use of ACE inhibitors and the ARA in preference to other antihypertensive agents. In these guidelines, any ad-blocker SRAA in particular (ACE inhibitors or ARA II) is preferably recommended as the treatment of choice. The cardiovascular

and renal results with RAS blockers for adults with diabetes have been evaluated in multicenter randomized controlled trials and meta-analysis (Bangalore *et al*, 2016).

In 2015 the guidelines of the American Diabetes Association recommend the SRA blockers (angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)) as first line treatment for people with diabetes and hypertension. In the same way, the 2013 American Society of Hypertension / International Society of Hypertension guides favors the SRA blockers as a first line treatment for people with diabetes. The National Kidney Foundation kidney-Outcomes Quality Initiative summarized in their clinical practice guidelines that "The hypertensive people with diabetes and chronic kidney disease stages 1-4 should be treated with an ACE inhibitor or an ARA, usually in combination with a diuretic." on the contrary, the European Society of Cardiology / European Society of Hypertension 2013 and The guidelines based 2014 (ESC Guidelines on diabetes, pre-diabetes and cardiovascular diseases developed in collaboration with the EASD 2014) in the evidence of the panel members of the eighth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension promoted to diabetes as a compelling indication of locking the RAAS and with presence of proteinuria or microalbuminuria. This set of institutions supported the cardioprotective effects greater and renoprotective of blockers of SRA in people with diabetes. The increase in the prevalence of terminal renal failure in DMII and hypertensive continues despite the fact that since at least two decades ago of renal protection programs intensified that includes an optimum control of blood pressure, the adequate glycemic control in diabetic patients, Stop smoking, physical activity and the extensive use of angiotensin-converting enzyme inhibitors or blockers of the renin-angiotensin-aldosterone system, both in the chronic renal failure in non-diabetics and diabetics is maintained.(Kropelin *et al*, 2015).

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the development and progression of the and as a mediator of the atherosclerotic disease, the endothelial dysfunction and oxidative stress, and its lock is considered the first-line therapy for the renal protection in diabetes. Studies of early initiation of locking the SRAA have shown delay in the emergence of the micro albuminuria, to date, these studies have been carried out in non-selected populations in large measure, and their limited success may reflect the fact that a smaller number of patients progress to ND. The microalbuminuria (> 30 mg/g) is the clinical seal used early and often of greater risk of diabetic nephropathy (ND), becoming a key marker for the risk prediction and monitoring of treatment in diabetes. In addition the ND is one of the most severe complications of diabetes in term of morbidity-mortality.

The study priority (prediction proteomics and inhibition of the renin angiotensin aldosterone in prevention of ND in patients with normoalbuminuria DMII), aims to address two clinical issues: firstly confirm that CKD273 can predict the development of microalbuminuria in a large cohort of patients with DMII normoalbuminuria; and secondly, to determine whether the early start of the antagonism of SRAA can reduce

the risk of transition to the microalbuminuria in individuals identified as participants of "high risk". (Lindhardt *et al*, 2016).

There are results that support the hypothesis that the content of medium-high glucose in the DMII increases the production of Ang II by the kidney, and above all, mesangial cells, resulting in the stimulation of the secretion of TGF-beta, giving rise to an increase in the synthesis and the reduction of the degradation of proteins of matrix, thereby producing the accumulation of matrix. This can be an important mechanism that relates the hyperglycemia and Ang II in the pathogenesis of diabetic nephropathy (Leehey, Singh, Alavi, & Singh, 2010) their deleterious effects can be blocked with the IECAS or ARA II.

The majority of the therapeutic drugs are directed to the track ACE / Ang II / ATIR to retard or delay the progression of renal lesion in diabetes, but could not reverse the progression of nephropathy. There is therefore a need to develop studies with medications such as IECAS or ARA II for the prevention of the progression of nephropathy in diabetics from the beginning of this disease, without waiting to present the microalbuminuria, it is known the tortuous path that awaits you in all aspects to the diabetic patient based on the evidence and published studies. You must show the benefits based on experiences that could be developed as a therapeutic target for the present and future clinical use (Viazzi, Leoncini, & Pontremoli, 2013).

Objective

The objective of this retrospective study is to assess the effect of IECAS or ARA II in patients with DMII normoalbuminuria and normotensive as nephroprotection and to prevent future complications irreversible, as its evolution in the diabetic nephropathy and hypertension; and reduce their impact on the health costs of the economies of many countries.

Methods and Analyzes

The present retrospective study describes the advantages of the use of the IECAS AND ARAII normoalbuminuria in diabetic patients and normotensive. The clinical trials with the objective of preventing the appearance of diabetic nephropathy by blocking the renin angiotensin system in patients normoalbuminuria almost have not been described. This could be reflected as the large fraction of patients normoalbuminuria are not at risk of progression initially to ND according to the studies described, which reduces the effect of nephroprotection studies in DM II of recent diagnostic. A classifier of specific risk based on the urine proteomics CKD273 (chronic renal disease (ESRD) 273) has shown that it can identify diabetic patients normoalbuminuria which later manifested to kidney disease, and also have the possibility of selection of patients with high risk for early intervention (Lindhardt *et al*, 2016). Avoid or prevent the development of microalbuminuria is the only criterion for evaluating available for early intervention with IECAS OR ARA II.

This study is being carried out with 116 patients of 20 - 70 years of age DM II from 2002 until the present normotensive and normoalbuminuria, 64 of whom are men and 52 women with multiple risk factors such as obesity, overweight diseases history family coronary, smoking and sedentary in its majority. In relation to medication, 91 patients receive

Lisinopril (ACEI) 5mg and 25 patients losartan (ARAI) 25mg in the evenings continuously from the time DM II is detected. In addition, motivational talks is continually held with patients and information provided with the purpose of establishing their diets (restriction of carbohydrates, fats and sodium), weight lost, in order to know their possible complications and make changes in their lifestyle, mainly exercises. 100% of the patients have renal ecusonography, hepatic and pancreatic, which according to the possibilities and years of sequela are put under control every 3 or 4 years. Are evaluated at the medical consultation every 6 months and yearly continuously.

Recent evidence establishes a relationship and association between the increase of blood pressure during sleep and the incidence of cardiovascular events at which to manage lisinopril or losartan in the evening according to our experience in this study will make primary prevention in diabetics from the start of their disease.

Only 3 patients taking lisinopril had cough so their medication had to be change to losartan. To date none of the patients of the study presented hypotension or other adverse effect. The previous examinations that were made and performed in addition to the glycemia, lipograma, HbA1C; are urine test to determine index albumin/creatinine, creatinine clearance (DCE) with calculation formulas CKD-EPI, Cockroft Gault and MDRD-4. Patients with arterial hypertension and renal compromise were excluded from the present study as well as those under 20 years of age and over 70 years.

Results

At present, the DMII represents a high percentage of the health budget in the whole world, so that prevention or delay of complications such as DN is of vital importance in order to avoid the costs of health increasingly growing. A patient with complications costs approximately six times more than that of a patient with DMII without complications. In addition, patients with DN are at risk of comorbidity, as well as cardiovascular complications and advanced kidney disease. The diabetes represents the main cause of terminal renal disease in most parts of the world. Any early intervention that can prevent or delay DN will therefore have a substantial impact on their economies (Nasri & Rafeian-Kopaei, 2015). An economic analysis of cost-benefit for health should be done after the results, and compare the costs associated with early treatment (normoalbuminuria) compared to potentially high costs in the treatment of patients with diabetic nephropathy, hypertensive, hiperlipidemicos or with ESRD.

As such, the prediction and prevention of microalbuminuria, (Schmieder et al., 2011) despite its limitations, is clinically important in the attention of our cases as a good noble proposal, practical, achievable, of low cost and with extraordinary results in primary prevention in the present and future of the patients with DM II. In addition the IECAS AND ARAII are first line of action due to its benefits in the treatment of diabetic patients with albuminuria, hypertension or renal insufficiency; because early use when the patient presents an irreversible damage micro and macro vascular with an uncertain future.

Until this date the 116 patients of the study do not have complications micro or macro vascular detectable by the

methods established for its diagnostics evaluation continuous assessments, waiting with optimism that in the next few years is maintained that balance the hemodynamic and re-evaluate the results in a not too distant future.

Conclusions

Our study current and impact with the aim of reducing statistically that diabetic patients evolve slowly but surely to the chronic kidney disease or death at an increasing pace; is to delay or prevent the kidney damage is taking possession of the diabetic patients in short time, which was not the case a few years ago. By blocking the angiotensin receptor or inhibit angiotensin converting enzyme and therefore avoid the microalbuminuria in conjunction with the various inflammatory signs renal and harmful cellular insults that can result in apoptosis of kidney cells and tubular, (Odegard et al., 2016) would achieve a better projection of life and reduce costs in the health budgets of many countries such as ours in the process of development.

I share my experience of more than 14 years using in low doses of lisinopril 5mg or Losartan 25mg ingested by the nights continuously in diabetic patients that they made their debut with the disease or normoalbuminuria of several years of evolution of their disease without hypertension. Possibly a study or investigation with many defects but with undeniable beneficial, even more in our country Ecuador that has epidemiological characteristics similar to many countries of the world, and where the dialysis units are not supplied to give palliative treatment for diabetic patients with CRF, causing exorbitant costs of millions of dollars in this chronic disease that is not transmissible. I would venture to say that doctors should begin to use in all diabetic II the drugs listed above for a long time and results checked.

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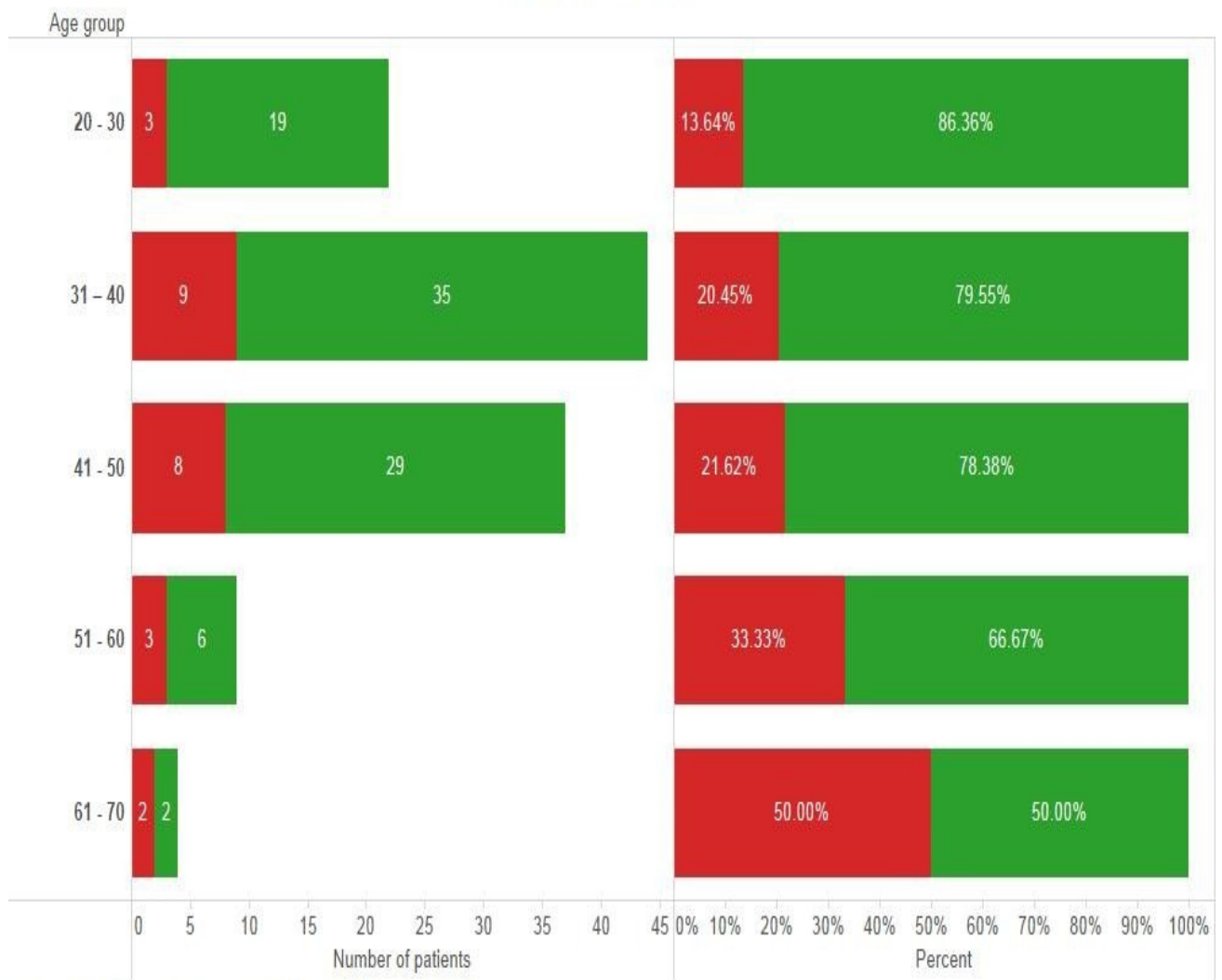
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Appendix
Figures

Use of ACE inhibitors or ARBs as Nephroprotection in diabetics type II normoalbuminuric normotensive by age group of starting treatment in the province of El Oro - Ecuador
Year 2002 - March 2016



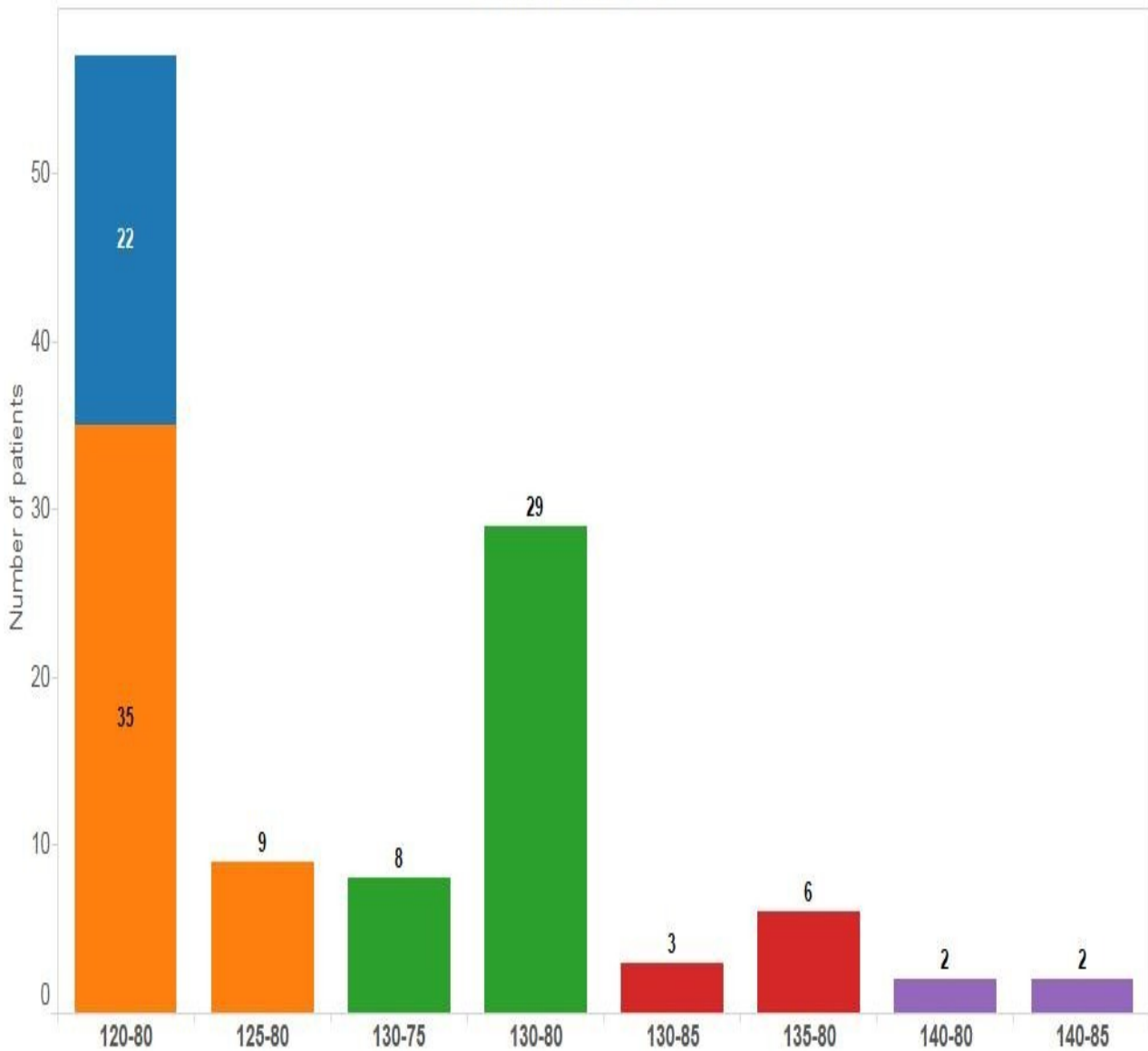
Source: private medical records and hospital Teofilo Davila
Prepared: Dr. Alexander Ojeda Crespo UACQS - UTMACH

Figure 1: Here they are described according to the age the number of patients admitted to the research on medication lisinopril (ACE) inhibitors and Losartan (ARBs).

Medication
■ Lisinopril 5mg
■ Losartan 25mg

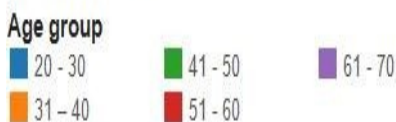
Use of ACE inhibitors or ARBs as Nephroprotection in diabetics type II normoalbuminuric normotensive by blood pressure of starting treatment in the province of El Oro - Ecuador

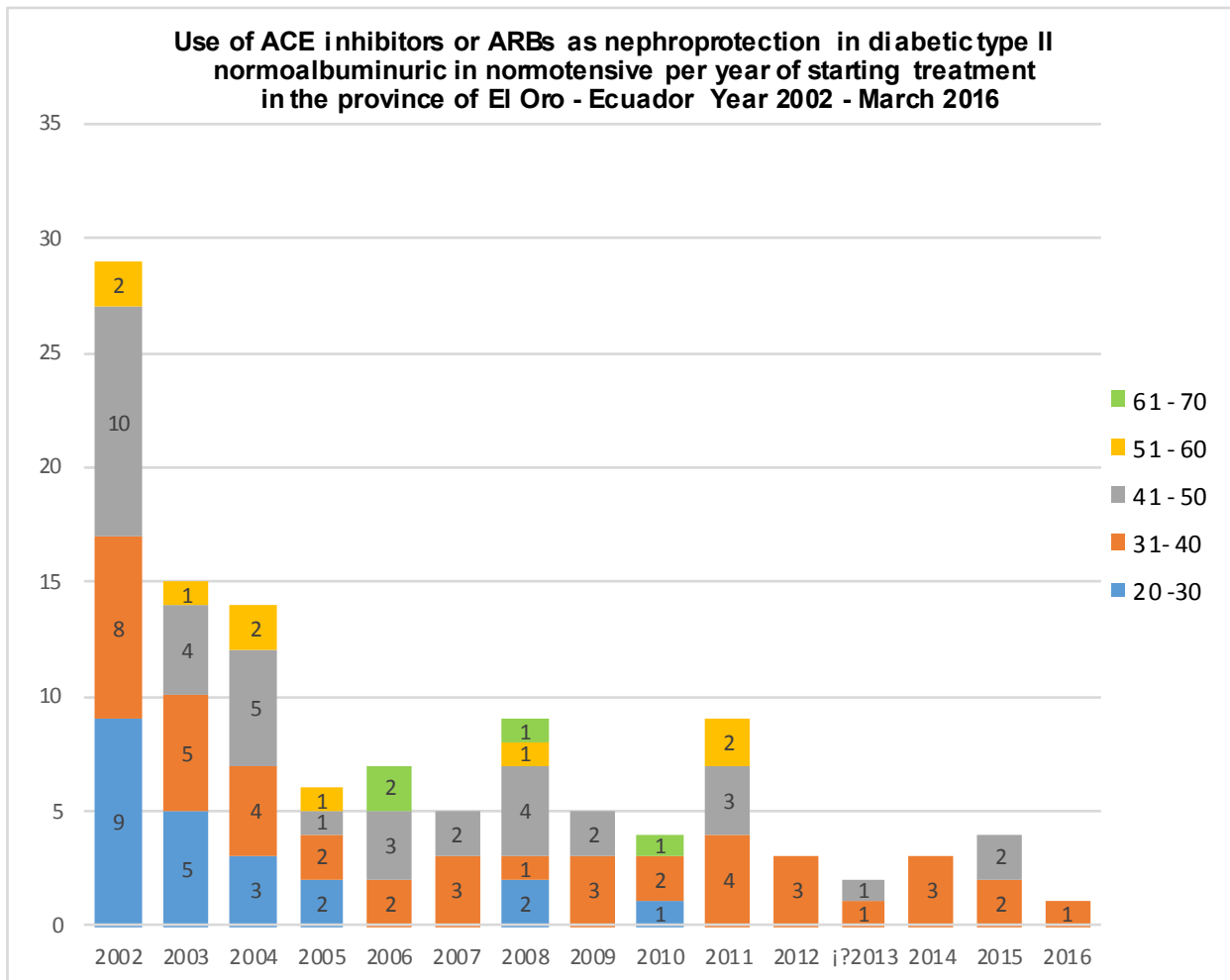
Year 2002 - March 2016



Source: private medical records and hospital Teofilo Davila
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Figure 2: Of different groups of patients by age group it states that 100 % of them started with pressures within normal limits set according to what the different existing guides.



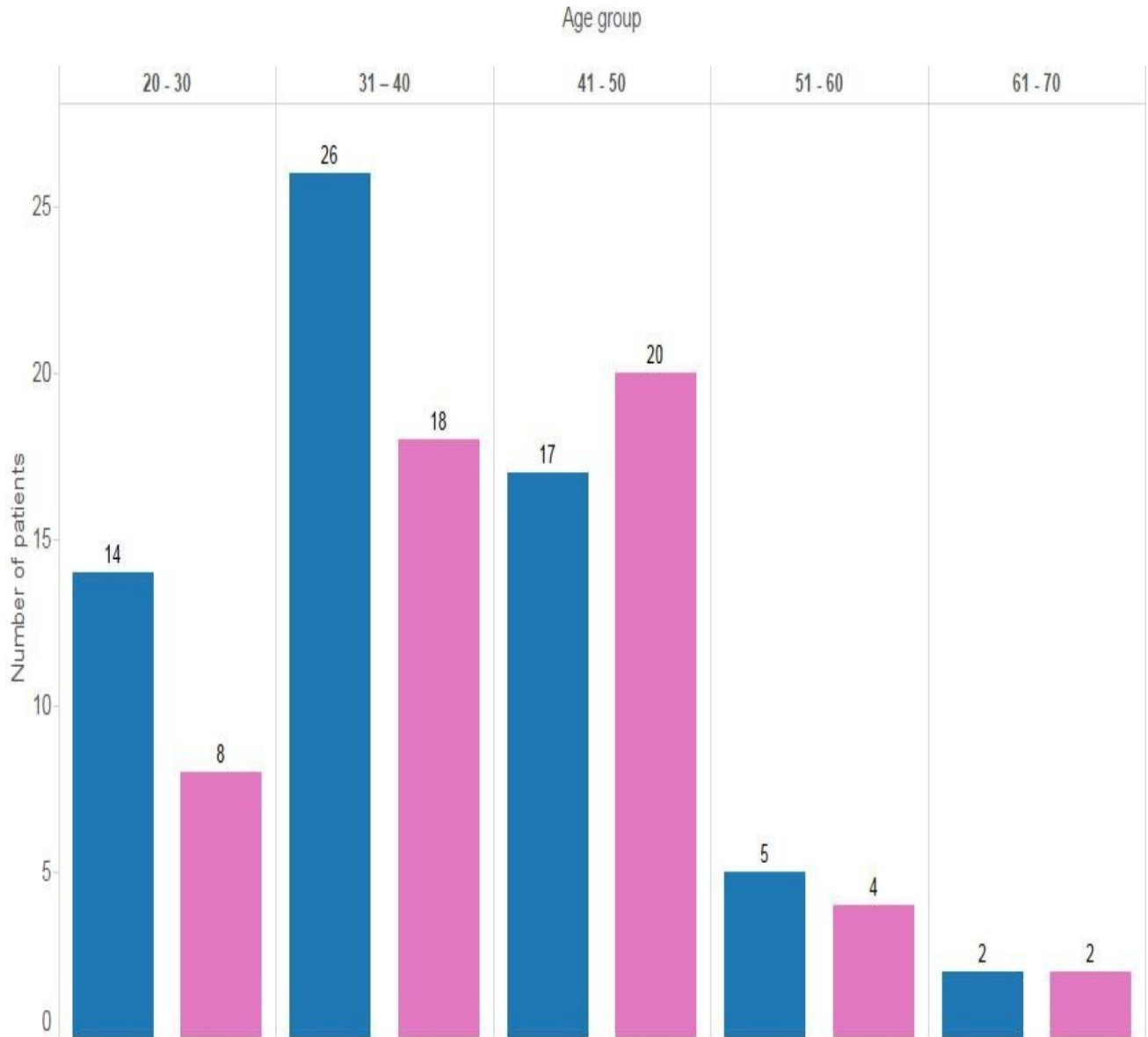


Source: private medical records and hospital Teofilo Davila

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Figure 3: It is plotted since 2002 when our research started with 29 patients; 2003 with 15 and so on. That is, until now 2016 the first patients are 14 ACE inhibitors and ARBs medicating and the respective controls and normotensive explained in detail normoalbuminuric remain.

**Use of ACE inhibitors or ARBs as Nephroprotection in diabetics type II normoalbuminuric
normotensive by sex of starting treatment in the province of El Oro - Ecuador
Year 2002 - March 2016**



Source: private medical records and hospital Teofilo Davila
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Sex
■ Mens
■ Women

Figure 4.