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The Effect of Angiotensin Converting Enzymes Inhibitors (ACEIs) on Type 2 Diabetes Mellitus (DM): Education on Prevention and Treatment

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Abstract: The incidence of diabetes is currently predicted to be about 6.4% worldwide, and in the past two decades alone there has been a dramatic rise in the diagnosis of type 2 diabetes mellitus. Diabetes Mellitus (DM) affects more than 170 million adults worldwide. Current World Health Organization (WHO) predicts that 350 million individuals worldwide will have diabetes, by the year 2030. 1 The risk of death among patients with diabetes mellitus is almost double that with people without diabetes mellitus. Diabetes has been found to be a major cause for many cardio-vascular diseases such as MI and angina. An internet-based search method was used in the systematic literature review of the study. This method included searching, collecting and evaluating stages. A manual review of the bibliographies of the important primary articles and review articles was also performed to identify any additional relevant studies. Results indicate that the use of ACEIs and ARBs has been found to be effective in preventing and delaying the onset of having new DM. Also it was found that ACEIs are better in preventing DM than the B-Blockers and diuretics. B-blockers and diuretics have been shown to decrease insulin sensitivity.

Keywords: Type 2 Diabetes Mellitus, Angiotensin, B-blockers, diuretics.

1. INTRODUCTION

The incidence of diabetes is currently predicted to be about 6.4% worldwide, and in the past two decades alone there has been a dramatic rise in the diagnosis of type 2 diabetes mellitus. Diabetes Mellitus (DM) affects more than 170 million adults worldwide. Current World Health Organization (WHO) predicts that 350 million individuals worldwide will have diabetes, by the year 2030. [1] The risk of death among patients with diabetes mellitus is almost double that with people without diabetes mellitus. Diabetes has been found to be a major cause for many cardio-vascular diseases such as MI and angina. An estimated 50 % of hypertension (HTN) patients are hyper-insulinaemic and about 75 % of patients with type 2 DM have HTN.

Diabetes mellitus (DM) is a group of metabolic diseases that are characterized by the increased level of glucose in the blood. The increased level of glucose can be either that the body is not having enough insulin secretion or is having a defect in the action of insulin. DM is defined as "a serious lifelong medical condition dealing with abnormal control of sugar in the bloodstream that causes a variety of symptoms series associated complications". [2] Diabetes mellitus type 2 is also characterized by insulin resistance and impaired insulin secretion; it is the predominant form and an independent risk factor for cardiovascular disease. [3]

Insulin resistance leads to a heightened sensitivity of the cardiovascular system to the adverse effects of the renin- angiotensin-aldosterone system.[4] Diabetes, especially type 2 DM which is associated with hypertension, aggravates the development of hypertension induced cardio-vascular diseases. Insulin

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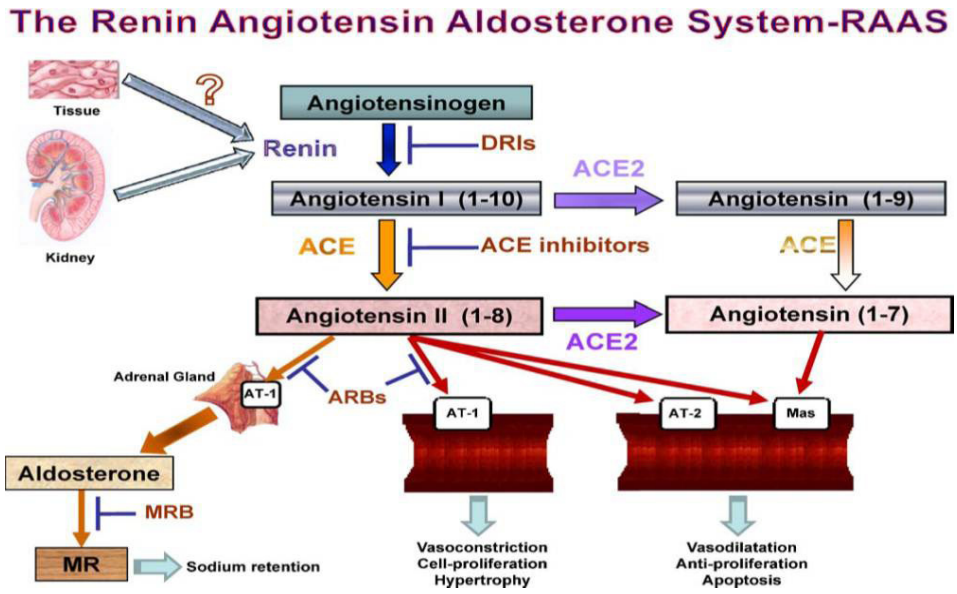
resistance has been shown to play critical role in atherosclerosis and HTN and therefore is found in the majority of people with these two conditions.[4]

Knowing and carefully identifying the causes of DM will help:

- Reduce the incidence of diabetes mellitus occurrence.
- Examine asymptomatic individuals at risk of DM to provide adequate guidance to them.
- Enhance care for patients who have been diagnosed with DM and provide them with a better life quality.



The renin angiotensin aldosterone system. ACE: angiotensin converting enzyme, ACE2: angiotensin converting enzyme 2, ARBs: angiotensin receptor blockers. AT-1, angiotensin receptor type 1, AT-2, angiotensin receptor type 2, AT-4, angiotensin (3–8) receptor type-4, MR: mineralocorticoid receptor, MRB: mineralocorticoid receptor blockers. Adopted from Staessen et al.[5]

2. METHODS

2. 1. Study Design

This study is a descriptive one and it comprises a systematic literature review which was carried out from December 2010 to August 2011. Procedures

An internet-based search method was used in the systematic literature review of the study. This method included searching, collecting and evaluating stages. A manual review of the bibliographies of the important primary articles and review articles was also performed to identify any additional relevant studies.

2.2. Search and data collection stage

This stage included the following steps:

- An extensive search had been conducted by using different databases, namely: Pub Med Central, ZETOC, EMBASE, Google (scholar), NHS National Library of Health, Cochran Library, Science Direct and JAMA Archive and Journals.
- In order to find the full text articles of some abstracts, the library inter-loan facility available at the University of Sunderland library had also been used.

- The following keywords had been used in the literature search: DM prevention, ACEIs in the prevention of DM2, RAS blockers and diabetes prevention, Angiotensin converting enzymes inhibitors and the prevention of diabetes mellitus type 2.
- The collected articles were all related to DM, RAS blockers and DM prevention, full text original articles (randomized clinical trial, case studies or systematic reviews) were used.

The inclusion criteria for the clinical trials were:

- All clinical trials should have been randomized.
- The number of the subjects in each trial should be more than 200 persons.
- The age of the participants should be up to 90 years old.
- The trials should have been done on humans not animals.

2.3. Analyzing and reviewing publications

Finally, these selected articles were thoroughly and critically read and evaluated. They were compared with each other, to produce the results presented in the systematic literature review given in this article.

3. RESULTS

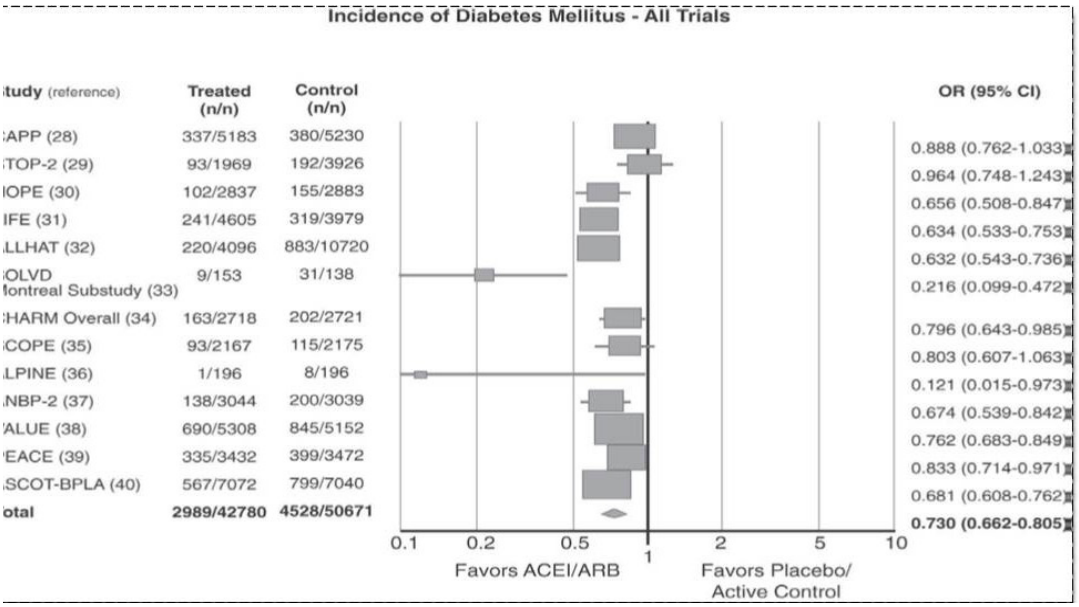
Randomized trials investigating the prevalence of new-onset type 2 DM in patients with RAS blockers:- [6]

Trial	Treatment	Sample size and age	Time years	Number of patients with new onset diabetes type 2	P-Value
LIFE (2002)	Losartan Atenolol	9193 patients 55-80 years	4.8 years	242/4605 losartan 320/ 4588 placebo	< 0.001
CAPP (1999)	Captopril Conventional medication	10985 25-66 years	6.1 years	337/4985 captopril 380/5027 conventional	0.039
ALLHAT (2002)	Chlorthalidone Amlodipine Lisinopril	42418 Mean age 66.9 years	4.9 years	302/6766 chlorthalidone 154/3954 amlodipine 119/4096 lisinopril	Chlorthalidone versus amlodipine 0.04 Chlorthalidone versus Lisinopril <0.001
VALUE(2004)	Valsartan Amlodipine	15245 =50years	4.2 years	690/7649 valsartan 845/7596amlodipine	< 0.0001
SOLVD (2003)	Enalapril Placebo	391 18-80 years	>3 years	1 patient in the enalapril 12 patients in the placebo	< 0.0001
HOPE (2000)	Ramipril Placebo	9297 >55years	5 years	102/2837 ramipril 155/2883 placebo	< 0.001
PEACE(2004)	Trandolapril Placebo	8290 >50years	4.8 years	335 / 3432 Trandolapril 399 / 3472 placebo	0.01
NAVIGATOR (2010)	Valsartan Placebo	9306 63.7±6.8 years	5 years	1532/4631 valsartan 1722/4675 placebo	<0.001
CHARM (2003)	Candesartan Placebo	7599 >18 years	3.2 years	163/2715candesartan 202/2721 placebo	< 0.02
ALPINE (2003)	Candesartan Hydro-chlorothiazide	392 55years	1 year	1/197 candesartan 8/196 hydro-chlorothiazide	0.03
STOP-2	ACEIs Conventional medication	6614 70-84 years	6 years	97/2213 conventional 93/2205ACEIs	0.77

The use of ACEIs and ARBs has been found to be effective in preventing and delaying the onset of having new DM. Also it was found that ACEIs are better in preventing DM than the B-Blockers and diuretics. B-blockers and diuretics have been shown to decrease insulin sensitivity.

DISCUSION, CONCLUSIONS and APPLICATIONS

Incidence of Diabetes mellitus in the clinical trials. Modified from Yusuf S, et.al.[7]



Almost half of the clinical trials trying ACEIs in HTN individuals resulted in a slight but significant reduction of new onset DM by increasing the insulin sensitivity as assessed by insulin stimulated glucose disposal during an euglycaemic hyper-insulinemic clamp. ACEIs have been shown to decrease both macro-vascular and micro-vascular complications of diabetes mellitus.

The exact mechanisms of the protective effect of ARBs are not entirely clear, but animals and humans studies have proved that RAS plays an essential role in glucose homeostasis. For that further researches and clinical trials are needed to determine the exact mechanism of RAS blockers in the prevention of Type 2 DM. The ONTARGET study pointed out that the combination of ARBs and ACEIS was associated with more side effects and with no significant benefit from that combination.

Based on the literature review on RAS blockers, we can reach the conclusion that patients who are pre-diabetic may be given RAAS blockers as a first line treatment in their hypertension. The literature showed that most of the conducted trials on B-blockers and RAS blockers were unclear as to whether the reduced risk of developing diabetes was associated to a benefit of the RAS blockers or related to the side effects of B-blockers. [8,9]

5. Limitations of the study

The results reported on in this project are mainly based on the findings of the research and studies I surveyed. However, further studies with collaborative efforts from all over the world are needed to investigate the mechanism of action of the preventive effect of renin angiotensin system blockers on diabetes mellitus.

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