HYPERTENSION IN TYPE 2 DIABETES: IMPACT OF GLUCOSE-LOWERING MEDICATIONS

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REVIEW ARTICLES

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INTRODUCTION

- **HYPERTENSION** OFTEN CO-EXISTS WITH OTHER **MODIFIABLE VASCULAR RISK FACTORS**

✓ **HYPERGLYCAEMIA**,

✓ **COMPLEX DYSLIPIDAEMIA**

✓ **SMOKING**

} IN PATIENTS WITH TYPE 2 DIABETES

→ **ABOVE 50%**

- GLOBALLY, **HYPERTENSION RATES** ARE HIGH

→ **ABOVE 75%.**

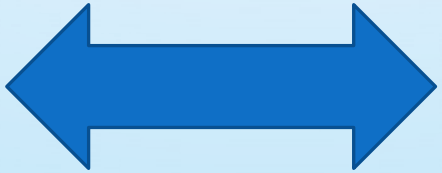
INTRODUCTION

- **OBSERVATIONAL STUDIES** :

ASSOCIATIONS OF **BP LEVELS** WITH **MEASURES OF GLYCAEMIC** CONTROL

ON THE **RISKS OF MORTALITY** AND **CORONARY HEART DISEASE** IN TYPE 2 DIABETES ARE

INDEPENDENT AND **ADDITIVE**

HYPERTENSION  **TYPE 2 DIABETES**

INTRODUCTION

❑PLAUSIBLE MECHANISMS :

STRONG ASSOCIATION BETWEEN **HYPERTENSION** AND **TYPE 2 DIABETES** :

1. PRODUCTION OF REACTIVE OXYGEN SPECIES

1. INSULIN RESISTANCE IN THE NITRICOXIDE PATHWAY

2. THE STIMULATORY EFFECT OF HYPERINSULINAEMIA ON SYMPATHETIC DRIVE

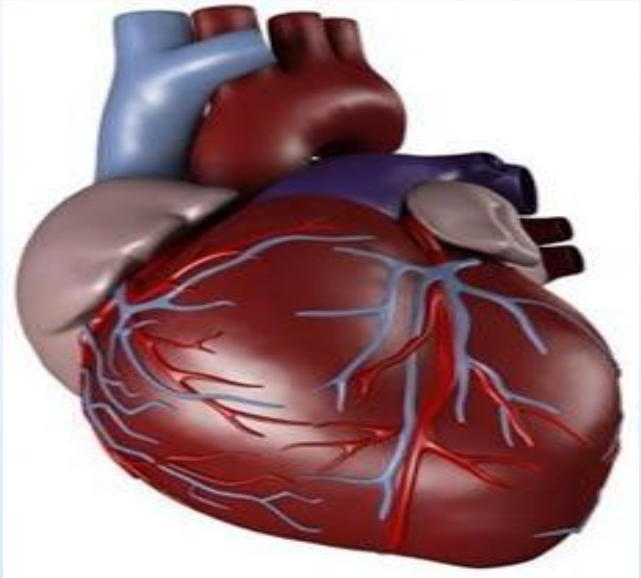
3. SODIUM-FLUID RETENTION

4. EXCITATORY EFFECT OF HYPERGLYCAEMIA ON THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

INTRODUCTION

- **THE RISK OF CARDIOVASCULAR DISEASE** → **FOUR-FOLD HIGHER**

(IN PATIENTS WITH BOTH **HYPERTENSION** AND **DIABETES**)



INTRODUCTION

- **IN TYPE 1 DIABETES, HYPERTENSION** → **DIABETIC RENAL DISEASE**
  - **ALBUMINUARIA** AND/OR
  - **DECLINING GLOMERULAR FILTRATION**

- **OVERWEIGHT OR OBESITY**
- **OLDER AGE**
- **LONGER DIABETES DURATION**

→ MAY BE ASSOCIATED WITH IMPAIRED **INSULIN SENSITIVITY** AND **ELEVATED BP** IN PATIENTS WITH **TYPE 1** DIABETES

INTRODUCTION

- **UKPDS** :PATIENTS IN THE **INTENSIVE BP TREATMENT** :

✓ **DEATH** RELATED TO DIABETES,

✓ **STROKE**

✓ **HEART FAILURE**

✓ **MICROVASCULAR ENDPOINTS**.

↓ **(SIGNIFICANT REDUCTIONS)**

- **CLINICAL STUDIES OF TYPE 2 DIABETES**: INTERVENTIONS TO :

IMPROVE **GLYCAEMIC CONTROL** IN CONCERT WITH EFFECTIVE **TREATMENT OF HYPERTENSION** :

✓AN **ADDITIVE BENEFICIAL IMPACT** ON → **VASCULAR COMPLICATIONS** .

INTRODUCTION

- IT IS WELL APPRECIATED : **ANTIHYPERTENSIVE MEDICATIONS** CAN HAVE EFFECTS :

✓ **PRODIABETIC**

✓ **NEUTRAL**

✓ **PROTECTIVE**

(ON BLOOD GLUCOSE LEVELS .)

- **LESS ATTENTION HAS BEEN PAID TO : THE EFFECT OF GLUCOSE-LOWERING DRUGS ON BP**

INTRODUCTION

- ✓**POSITIVE**
- ✓ **NEUTRAL**
- ✓**NEGATIVE**

} **EFFECT ON BP HAVE BEEN REPORTED**

IN THIS ARTICLE :

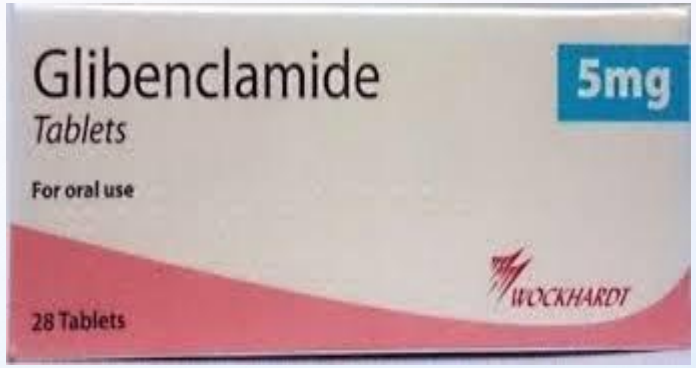
THE EFFECTS OF **GLUCOSE-LOWERING MEDICATION** **ON** **BP** ARE REVIEWED .

GLUCOSE-LOWERING MEDICATIONS:

1. SULFONYLUREAS
2. MEGLITINIDES
3. BIGUANIDES
4. [ALPHA]-GLUCOSIDASE INHIBITORS
5. THIAZOLIDINEDIONES
6. DPP-4 INHIBITORS
7. SGLT-2 INHIBITORS
8. GLP-1 RECEPTOR AGONISTS
9. INSULIN

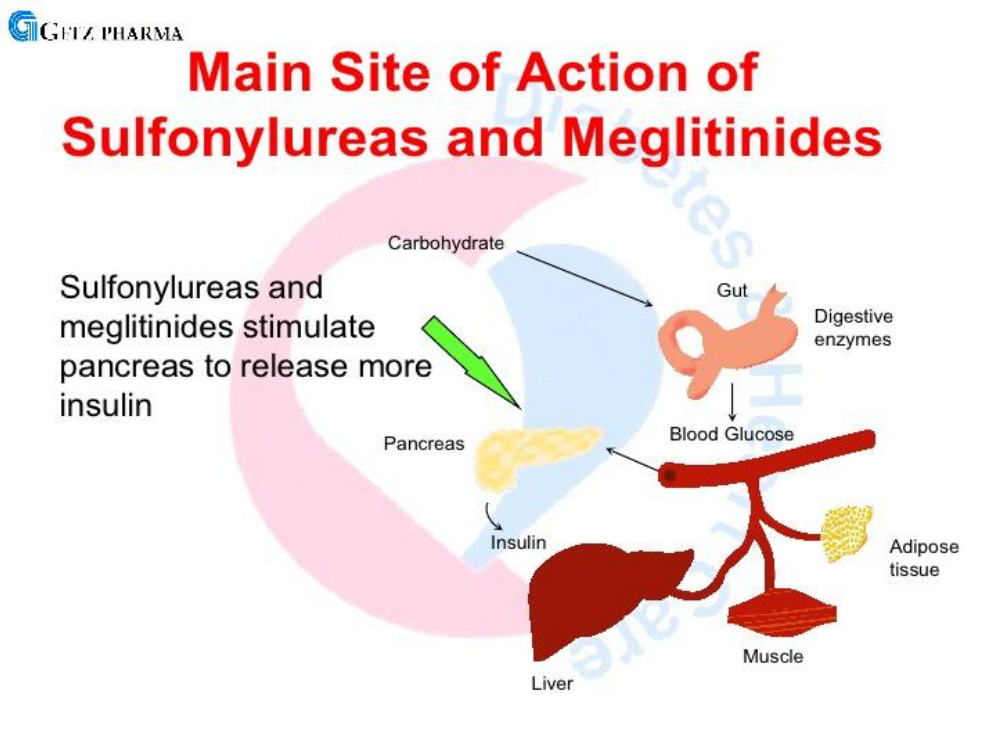
1 .SULFONYLUREAS :

- GLIBENCLAMIDE
- GLIMEPIRIDE
- GLIPIZIDE
- CHLORPROPAMIDE



SULFONYLUREAS

- STIMULATE THE **RELEASE OF INSULIN FROM THE [BETA]-CELLS** OF THE PANCREATIC ISLETS .



SULFONYLUREAS

- GENERALLY CONSIDERED TO BE **NEUTRAL** WITH RESPECT TO THEIR EFFECTS **ON BP.**
- **SULFONYLUREA-ASSOCIATED :**

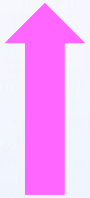
✓ ↑ WEIGHT GAIN

✓ ↑ ADIPOSE TISSUE

} **HAVING THE POTENTIAL TO : BP** ↑

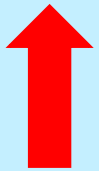
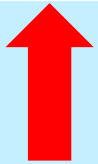
SULFONYLUREAS

- THERE HAVE LONG BEEN CONCERNS THAT :

✓**SULFONYLUREAS** : THE **RISK OF CARDIOVASCULAR** EVENTS 

CONTROVERSIAL ?

SULFONYLUREAS

Available data on the effects of sulfonylureas on BP range	
glibenclamide	
glipizide	
chlorpropamide	
glimepiride	neutral effects

SULFONYLUREAS

CHLPROPORAMIDE: SIGNIFICANTLY :

- ↓ **MEAN HB A_{1C}** ⟶ THAN **GLIBENCLAMIDE** GROUP

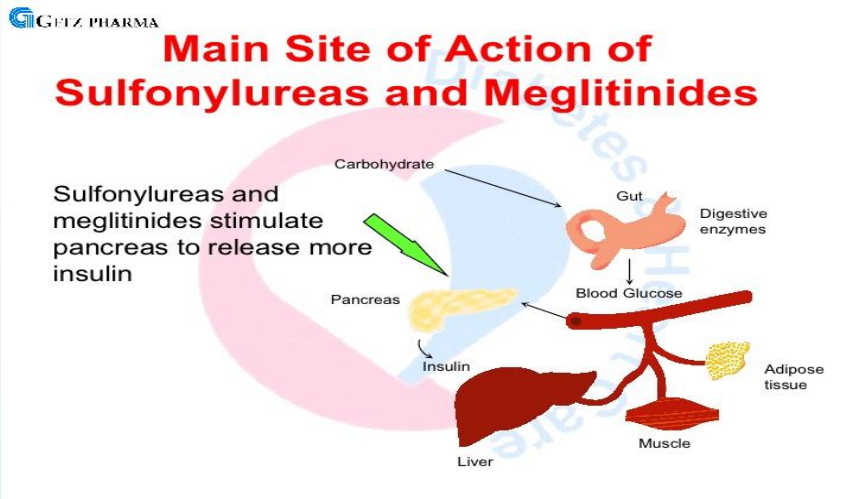
2 .MEGLITINIDES :

- **REPAGLINIDE**

- **NATEGLINIDE**

MEGLITINIDES :

- **INCREASE INSULIN SECRETION**, IN PARTICULAR, THE EARLY PHASE OF INSULIN RELEASE .



✓**WEIGHT GAIN** (SIMILAR TO SULFONYLUREAS).

✓THE EFFECTS ON BP **HAVE NOT BEEN WELL QUANTIFIED** .

MEGLITINIDES :

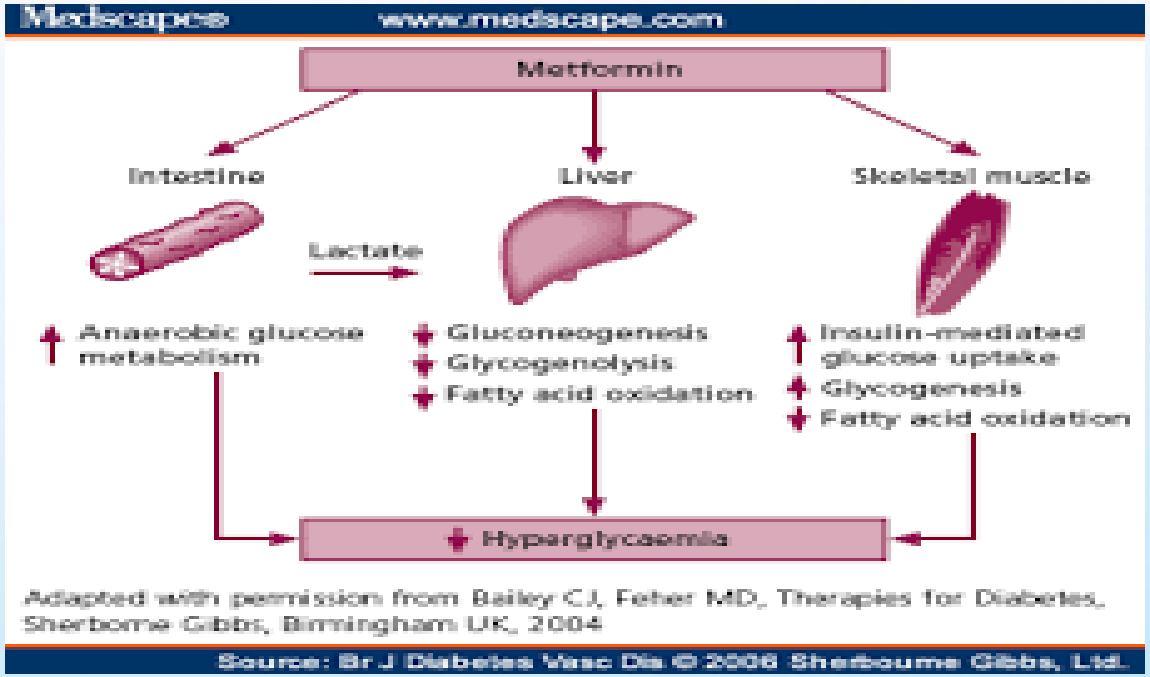
- **IN A COMPARATIVE STUDY** IN NONOBESE PATIENTS WITH TYPE 2 DIABETES : **NONGLYCAEMIC VASCULAR RISK BIOMARKERS :**

1. LEVELS OF **TNF** [ALPHA]
2. **PLASMINOGEN ACTIVATOR INHIBITOR**-1 ANTIGEN
3. TISSUE-TYPE PLASMINOGEN ACTIVATOR **ANTIGEN**
4. **VON WILLEBRAND FACTOR**
5. SOLUBLE INTERCELLULAR ADHESION **MOLECULE-1**
6. SOLUBLE E-SELECTIN

SIGNIFICANTLY ↓ DURING **METFORMIN** VERSUS **REPAGLINIDE** THERAPY FOR SIMILAR DEGREES OF GLYCEMIC CONTROL

3 .BIGUANIDES :

- **METFORMIN**



BIGUANIDES :

- **IN UKPDS :**

A RELATIVELY SMALL GROUP OF OVERWEIGHT PATIENTS (***N*=342**)

WITH RECENTLY DIAGNOSED TYPE 2 DIABETES :

WHO WERE RANDOMIZED TO **METFORMIN MONOTHERAPY** :

1. **MYOCARDIAL INFARCTION** (39% REDUCTION)
2. **CORONARY DEATHS** (50% REDUCTION)
3. **ALL-CAUSE MORTALITY**

(RELATIVE TO **DIET** THERAPY)

BIGUANIDES :

- **IN UKPDS**
  - **MECHANISMS** THROUGH WHICH **METFORMIN** WAS ASSOCIATED WITH **CARDIOPROTECTION** : **UNCERTAIN**
  - **IMPROVEMENTS** IN
    1. **LIPIDS**
    2. **THROMBOSIS**
    3. **BLOOD FLOW**

    ] HAVE BEEN POSTULATED .
  - **WEIGHT NEUTRALITY OR MODEST WEIGHT** .
  - HAVE **INSULIN-SENSITIZING** PROPERTIES
  - **IMPROVED INSULIN ACTION IN SKELETAL MUSCLE** APPEARS TO BE A SECONDARY EFFECT TO LOWER **GLUCOSE CONCENTRATIONS** RESULTING FROM **REDUCTIONS IN HEPATIC GLUCOSE PRODUCTION**

BIGUANIDES :

- **A SYSTEMATIC REVIEW : METFORMIN :**

➢ **IN PATIENTS WITH TYPE 2 DIABETES** : HAD **NO INTRINSIC EFFECTS** ON BP .

➢ **NONDIABETIC PATIENTS** WITH **ST** ↑, **MI** TREATMENT WITH **METFORMIN** FOR **4 MONTHS :**

✓ **MODEST IMPROVEMENT** IN THE **CARDIOVASCULAR RISK PROFILE**

COMPARED WITH **PLACEBO**

4 .[ALPHA]-GLUCOSIDASE INHIBITORS :

- **ACARBOSE**

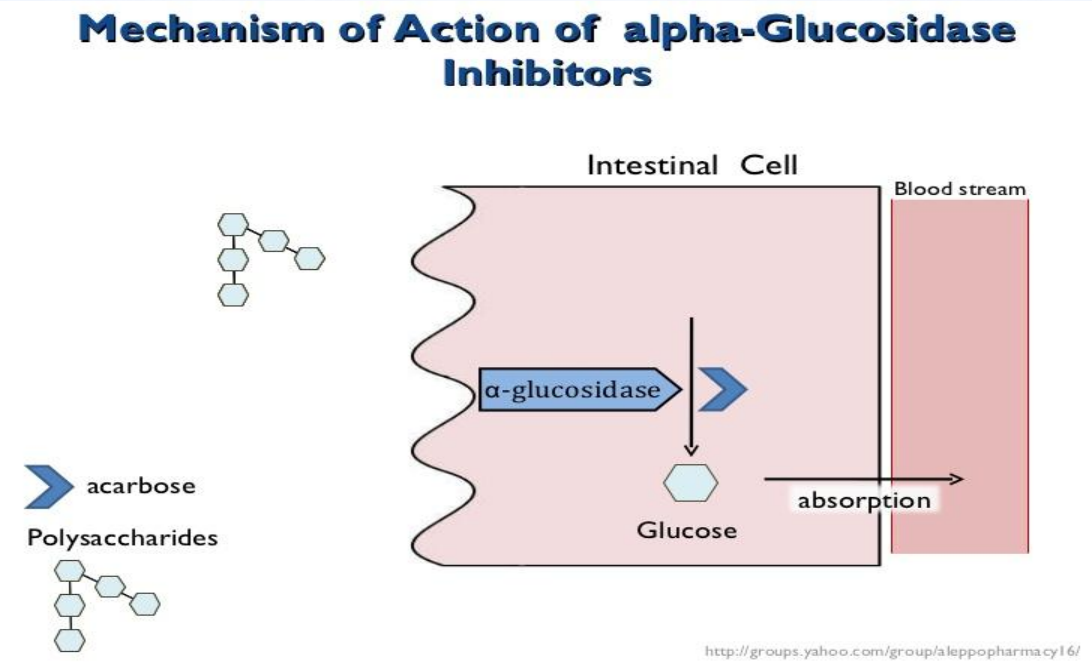
- **VOGLIBOSE**

- **MIGLITOL**

[ALPHA]-GLUCOSIDASE INHIBITORS :

- **RETARD GLUCOSE ABSORPTION** FROM THE INTESTINE : ↓ **POSTPRANDIAL GLUCOSE**

  IN PATIENTS WITH TYPE 2 DIABETES



- DATA ON THE EFFECTS ON BP ARE LARGELY CONFINED TO **ACARBOSE** .

4 .[ALPHA]-GLUCOSIDASE INHIBITORS

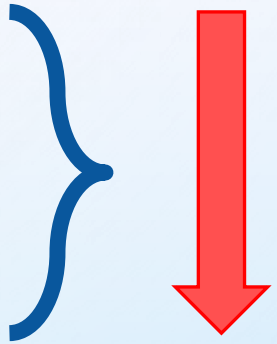
- **ACARBOSE : BENEFICIAL EFFECTS ON :**

1. **BODY WEIGHT,**
2. **TRIGLYCERIDES,**
3. **MARKERS OF LOW-GRADE CHRONIC INFLAMMATION**
4. **BP**

[ALPHA]-GLUCOSIDASE INHIBITORS :

- **STOP-NIDDM** : IN THE STUDY TO **PREVENT** NONINSULIN-DEPENDENT-DIABETES-MELLITUS TRIAL :
- **ACARBOSE** :

1. PROGRESSION OF **INTIMA MEDIA THICKNESS,**
2. INCIDENCE OF **CARDIOVASCULAR EVENTS**
3. THE INCIDENCE OF **NEWLY DIAGNOSED HYPERTENSION**



- **34%** RELATIVE RISK ↓ IN THE **INCIDENCE OF NEW CASES OF HYPERTENSION** IN PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE **(IGT)** COMPARED WITH **PLACEBO**

5 .THIAZOLIDINEDIONES :

- **PIOGLITAZONE**
- **TROGLITAZONE**
- **ROSIGLITAZONE**

THIAZOLIDINEDIONES :

- **THIAZOLIDINEDIONE :**
- **IMPROVE INSULIN ACTION .**
- **MODEST BP EFFECTS**

- **REDUCTIONS IN BP:** FAVOURABLE EFFECTS ON **:**

OTHER CARDIOVASCULAR RF

(ANIMAL MODELS AND CLINICAL STUDIES)

THIAZOLIDINEDIONES :

THIAZOLIDINEDIONE : **BODY WEIGHT** ↑

(PARTICULARLY IN COMBINATION WITH INSULIN THERAPY)

- PART OF THE GAIN IN BODY WEIGHT IS ATTRIBUTABLE TO :

➢ **WATER RETENTION**, WHICH CAN MANIFEST AS **OEDEMA WITH A RISK OF HEART FAILURE** IN VULNERABLE PATIENTS

THIAZOLIDINEDIONES :

- ↓ ~**4–5 MMHG** IN SYSTOLIC AND **2–4 MMHG** IN DIASTOLIC BP HAVE BEEN REPORTED .
- **TROGLITAZONE**-INDUCED IMPROVEMENTS IN BP :

  IN PATIENTS WITH TYPE 2 DIABETES WERE ATTRIBUTED TO : **VASODILATORY EFFECTS** .

- **PIOGLITAZONE** → BP ↓ **3–5 MMHG AFTER 12 MONTHS** OF THERAPY WHEN ADDED TO EITHER **GLIMEPIRIDE OR METFORMIN**

- **ROSIGLITAZONE** → **SIMILAR EFFECTS** REPORTED : IN NONDIABETIC HYPERTENSIVE PATIENTS AND IN PATIENTS WITH TYPE 2 DIABETES

  (WHICH CORRELATE WITH **IMPROVEMENTS IN INSULIN SENSITIVITY**)

6 .DPP-4 INHIBITORS :

- **SITAGLIPTIN (ZIPTIN)**

- **VILDAGLIPTIN**
- **SAXAGLIPTIN**
- **LINAGLIPTIN**
- **ALOGLIPTIN**

DPP-4 INHIBITORS :

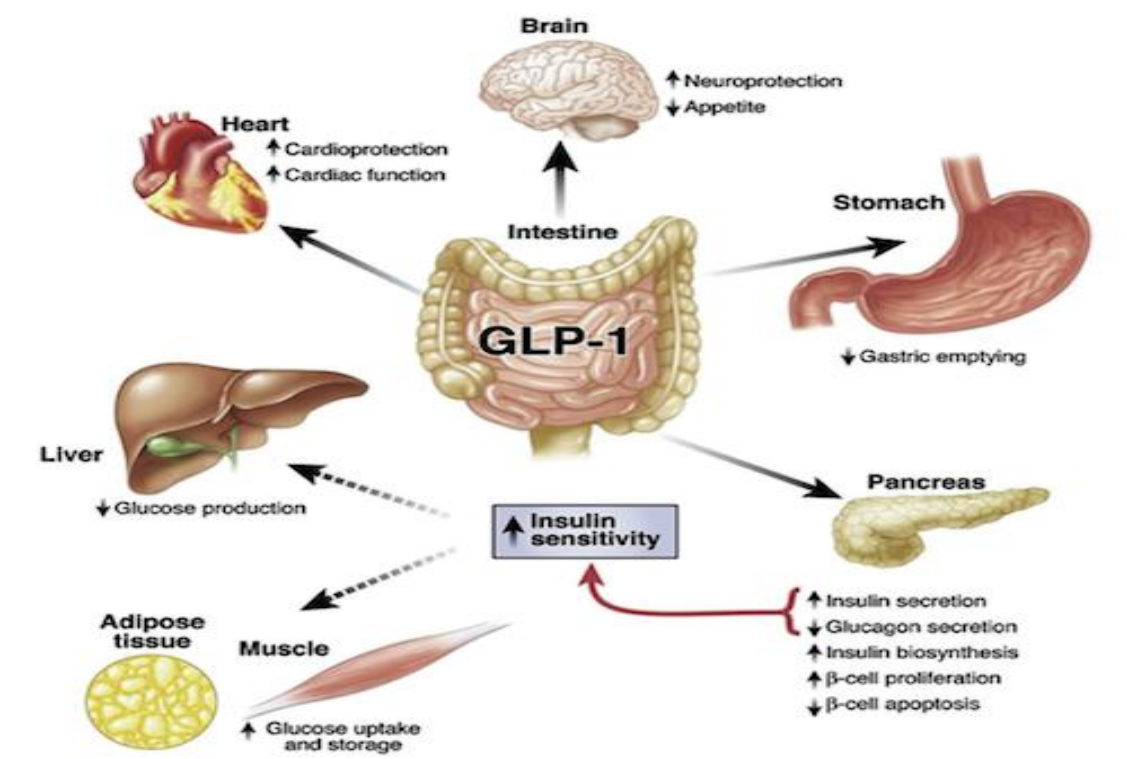
- THESE DRUGS HAVE **GENERAL EXCELLENT TOLERABILITY** PROFILES

DPP-4 INHIBITORS :

1. WEIGHT NEUTRAL

DPP-4 INHIBITORS :

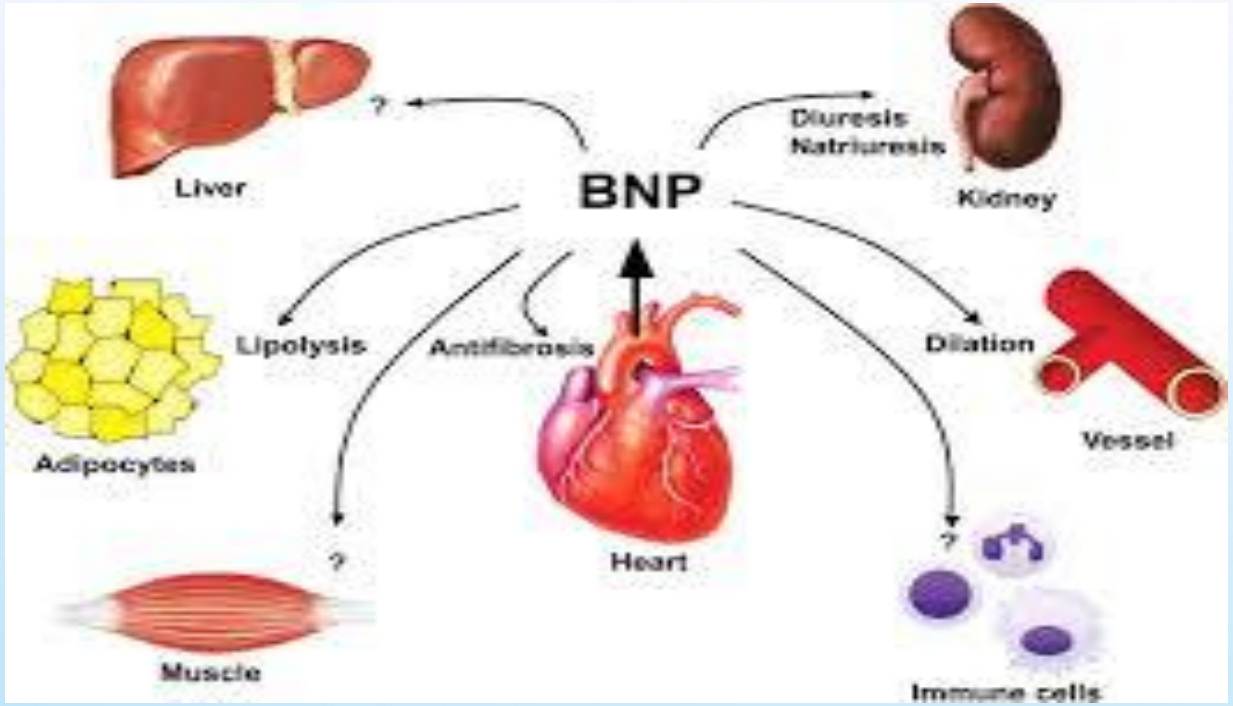
2. THE BREAKDOWN OF THE INCRETIN HORMONES GLP-1 AND GIP



DPP-4 INHIBITORS :

3 . ↓ **THE DEGRADATION** OF **SEVERAL VASOACTIVE PEPTIDES**

INCLUDING THE VASODILATOR **BRAIN NATRIURETIC PEPTIDE**



DPP-4 INHIBITORS :

- **CVOTS** (**CARDIOVASCULAR OUTCOME TRIALS**) :

IN PATIENTS WITH TYPE 2 DIABETES AT HIGH RISK OF CARDIOVASCULAR EVENTS :

SAXAGLIPTIN, ALOGLIPTIN AND SITAGLIPTIN : INDICATED THAT :

DPP-4 INHIBITORS : ↓ BP IN PATIENTS WITH DIABETES

DPP-4 INHIBITORS :

- A RECENT **SYSTEMATIC REVIEW** AND **META-ANALYSIS** OF **15** TRIALS :

  DPP-4 INHIBITORS ACHIEVED **GREATER** ↓ :

1 . **SYSTOLIC BP** (MEAN DIFFERENCE, -3.04 MMHG;)

2 . **DIASTOLIC BP** (MEAN DIFFERENCE, -1.47 MMHG)

(COMPARED WITH **PLACEBO** OR **NO TREATMENT**)

DPP-4 INHIBITORS :

- **REPORTED IN RECENT CVOTS :**

✓ WHETHER DIFFERENCES IN **DIURNAL BP CONTROL** ARE OF RELEVANCE TO THE RISK OF **DEVELOPING HEART FAILURE** BETWEEN **INDIVIDUAL DPP-4 INHIBITORS** REMAINS : **UNCERTAIN** .

✓ **SAXAGLIPTIN** ASSOCIATED WITH AN : ↑ **RISK OF HOSPITALIZATION** FOR **HF** .

DPP-4 INHIBITORS :

✓**MORE DETAILED EVALUATION** USING THE GOLD STANDARD

OF **24-H AMBULATORY BP MEASUREMENTS** IN CAREFULLY

DESIGNED COMPARATIVE STUDIES WOULD BE REQUIRED TO

TEST THIS HYPOTHESIS .

The effects on BP

Sulfonylureas	
Meglitinides :	have not been well quantified
Biguanides	no intrinsic effects on BP
[alpha]-Glucosidase inhibitors :	
Thiazolidinediones	
DPP-4 inhibitors :