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Pharmacogenetics and the Practice of Medicine

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Abstract: *Drug–Drug-Interactions (DDI) are a well-known cause of adverse drug events [1].The number of potential drug interactions increases exponentially with the number ofTaken drugs, making it hard to consider all drug interactions in polypharmacy patients.Drug interaction databases can help the clinician to recognize and avoid adverse drugInteractions.[2] A phenomenon can be observed in dailypractice, though: even if a Database warns about a clinicallyrelevant DDI, the patient may not show any signs of aGiven DDI. This discrepancy between scientific evidence and clinical reality causes alertFatigue and also raises conflicts between the DDI warning pharmacists and no adverse Drug event-observing physicians.*

Keywords: Drug–Drug-Interactions

I. INTRODUCTION

Drug–Drug-Interactions (DDI) are a well-known cause of adverse drug events [1].The number of potential drug interactions increases exponentially with the number of Taken drugs, making it hard to consider all drug interactions in polypharmacy patients. Drug interaction databases can help the clinician to recognize and avoid adverse drug Interactions.[2] A phenomenon can be observed in daily practice, though: even if a Database warns about a clinically relevant DDI, the patient may not show any signs of a Given DDI. This discrepancy between scientific evidence and clinical reality causes alert Fatigue and also raises conflicts between the DDI warning pharmacists and no adverse Drug event-observing physicians .[2]

Pgx testing has become more popular over the last decade, but it is not yet a routine Test, except in oncology. However, there is growing evidence that large proportions of Patients are affected by an actionable genotype—a genotypes where a change in prescribing May be indicated. The evidence for Drug–Gene-Interactions (DGI) exists for many drug–Gene pairs already. In pediatric patients, for example, the annual prescribing prevalence Of at least one level A drug (recommendations for drugs available with high evidence Regarding a particular genotype) ranges from 7987 to 10,629 per 100,000 patients [3]. Turner Analyzed the data from non-S Televation myocardial infarction patients (n =1456)and Found that 98.7%ofthepatients had at least one actionablegenotype.[4]The ultimate goal for pharmacogenetics and pharmacogenomics is the development of personalized medicine, defining the population diversity of polymorphisms, genetic mutations, and gene expression profiles of clinical interest, thereby facilitating prescription of drugs based on a patient's individual genetic or biological profile, or the individual genetic profile of his/her tumor. In oncology, pharmacogenetics and pharmacogenomicshavealreadybeenappliedtopredictcancersusceptibility,tumorprogression and recurrence, patient survival, and response to and toxicity associated with traditional chemotherapy treatments.[2]

II. REVIEW LITRATURE SURVEY

Thompson J.et, al-Pharmacology Adverse drug reaction201027(12),2233-2243
This review was preceded by a dose-response and pharmacodynamic evaluation of IV or IP doses of MDL-28170 with regard to ex vivo inhibition of calpain 2 activity in harvested brain homogenates.

Hahn M. Roll SC et, al-The influence of pharmacogenetics on the clinical relevance of Pharmacokinetics drug-drug interaction2021;14(5)-159-160
This review discusses the current evidence of drug–drug–gene interactions, as well as drug–gene–gene interactions. Phenoconversion is explained, the and methods to calculate the phenotypes are described.

Zhang Q et,al-A prospective Studyof biomarker garded chemotherapy in Patients with non small cell lung cancer2014;74(4)839-846

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This review Purpose To assess the therapeutic value of biomarker-guided chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). Methods Eighty-five NSCLC patients at stage IIIb or IV were divided into two groups based on the feasibility of biomarker analysis.

PorterSRet,al-Oralulcersandit'srelevancetosystemicDisorder.2005;21(4):295-306

This review article by Porter SR and Leao JC likely discusses the different types of oral ulcers and their possible causes, as well as the importance of recognizing oral ulcers as a potential sign of underlying systemic disease. It may also provide information on the diagnosis and management of oral ulcers.

Gaidhani,K.A.et,al-WorldJournalofPharmaceuticalreasearchFormulation2021;2(5):1685-1703.

This review article provides a comprehensive overview of lyophilization, a technique used to preserve biological materials like pharmaceuticals, foods, and vaccines. It covers the principles, advantages, and applications of this process

Objective

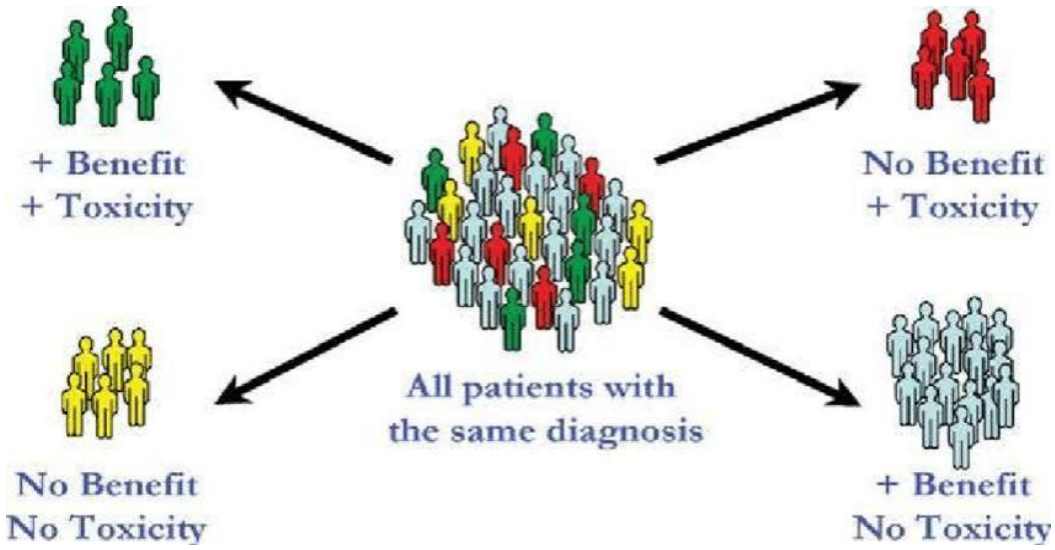

Fig 1-of Objective for Pharmacogenetics

Pharmacokinetic Drug–Drug Interactions

In the past, the magnitude and clinical importance of drug interactions was often Neglected.[2] because of overalerting DDIs in clinical practice[5]. The CYP-inhibitory Or -inducing potential of a drug and the specificity of the potential victim drug Must be considered . CYP perpetrator drugs are inhibitors or inducers of CYP Enzymes. CYP perpetrator drugs affect the metabolism of victim drugs (CYP substrates) And lead to an increase or decrease in serum concentrations of the victim drugs. The Food And Drug Administration categorizes CYP inhibitors or inducers as strong, moderate, or Weak based on pharmacokinetic DDI studies .[6] CYP inhibitors that were categorized As ―strong‖ (> fivefold increase in area under the plasma concentration–time curve (AUC) Or > 80% decrease in clearance) or ―moderate‖ (> twofold but < fivefold increase in the AUC Or 50–80% decrease in clearance) and CYP inducers categorized as ―strong‖ (≥ 80% decrease In AUC) or ―moderate‖ (50–80% decrease in AUC) can be regarded as clinically relevant. Several tables of drugs as substrates, inhibitors, and inducers of drug- metabolizing CYP Enzymes have been published in the past[7]. The categorization into strong, moderate.

Drug Toxicity and Target Polymorphism

Genetic polymorphism not only influences antibody drug efficacy But may also contribute to drug toxicity. In a recent study of HER2 Genetic polymorphism in breast cancer patients receiving the antiHER2 Mab trastuzumab-based treatment, a potential link between The development of cardiotoxicity and HER2 polymorphism was Observed [8]. In this

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small size study with genotype information Available for 56 patients, all 5 patients who developed cardiotoxicity after trastuzumab treatment carriedtheHER2- 655Val/Ile (valine/isoleucine) phenotype, with no apparent link to anthracycline Treatment. It is still preliminary to conclude that the HER2-655Val/Ile Allele is predictive for cardiotoxicity associated with trastuzumab Treatment, and the presence of this allotype and its association With cardiotoxicity need to be further analyzed in larger studies. If validated, this correlation between HER2 polymorphism and Cardiotoxicity may provide a means of managing trastuzumab Toxicity in breast cancer patients by avoiding treatment of a high Development.

Risk subgroup.

There is also evidence suggesting that cardiotoxicity of trastuzumab is further enhanced if it is given together with anthracycline Chemotherapy. Cardiotoxicity due to anthracycline chemotherapy Is also affected by the genetic background of the host. The cardiotoxicity is mediated by iron, and geneticstudies in mice reveal Worsened cardiotoxicity when the HFE gene, defective in hereditary is knocked out .[9]

III. BIOLOGICAL FACTORS MODIFYING DRUG RESPONSE

Age

The elderly and children are often unusually Sensitive to drugs due to reduced efficiency and Immaturity, respectively, of systems involved in Drug handling. In the elderly, the capacity to Absorb, metabolize and eliminate drugs is frequently reduced. Gastric pH is increased and Gastric motility is decreased with increasing age[10]. In addition, many elderly patients suffer from Multiple illnesses and receive concurrent medications, which may have the potential to interact With each other. These could partly explain the Increase with age in the incidence and severity of Adverse effects. In newborn infants, particularly premature infants, many drug metabolizing Enzyme systems are underdeveloped. The renal Excretion of drug is also depressed [10]. These Age-related changes in physiological functions In¯uence the kinetics of drugs and manifest as altered drug response.

Gender

Gender appears to bea relatively minor factor Contributingto differences in drugresponse. A Numberof drugs show sex-related differences in Pharmacokinetics. For example, the elimination Half-life of o¯oxacin was shown to be shorter And peak plasma concentration higher in women Than men[2]. Gender differences in pharmacokinetics may be due to differences in body Composition, weight, ratio of lean to fat body Mass, hormonal status, gastric motility and Secretion, and hepatic metabolism [11]. Women Generally have more adipose tissue, secrete less Gastric acid and have slower gastric emptying Thanmen. The greater blood pressure response To amlodipine in women may be explained by Sex-related pharmacodynamic differences [4].These differences may also explain the higher Incidence of adverse effects observed in women Compared to men [12].

Disease

Drugs are usually administered to people in whom Aphysiologicor biochemical processis altered by Disease. For instance, hepatic blood ¯ow and Extraction are altered in patients with cirrhosis.Drug disposition is thereby in¯uenced by concurrent disease, with hepatic and renal diseases being The major concern. Hepatic drugelimination and The conversion of prodrug, such as enalapril and Perindopril, may be substantially reduced in Chronic liver disease [10]. Drug±plasma protein Binding may be decreased or increased in in¯ammatory, renal or liver diseases[13]. In patients with Hepatic or renal insuf®ciency, drugs eliminated by Those organs must be used with caution and dosage Adjustment may be required

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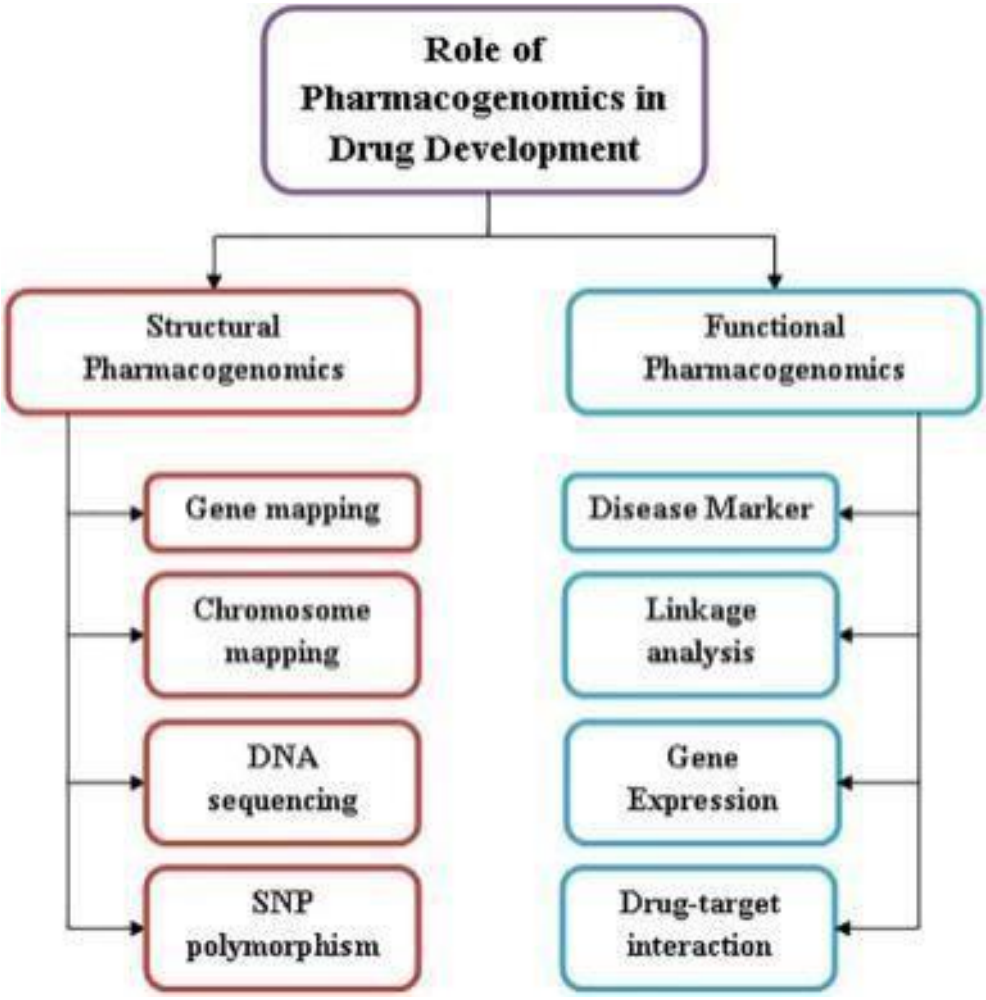

Fig 2. Role of pharmacogenomics in drug development

Applications

Pharmacogenomics and personalized medicine

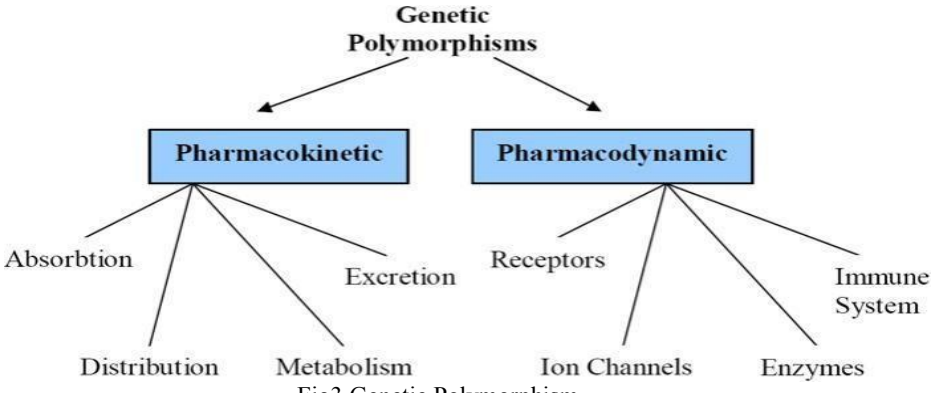

Fig3.Genetic Polymorphism

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Advantages of Pharmacogenetics

To Predict a patient's response to Drugs
To develop—Customised Prescriptions
To minimize or eliminate adverse Events
To Improve efficacy and patients compliance
To Improve rational drug Development
Pharmacogenetics test need only be conducted once during the lifetime

Drug–Drug–Gene Interactions (DDGIs) and Phenoconversion

Phenoconversion is the conversion of a genetic phenotype (i.e., PM, IM, NM, and UM) Into a different phenotype by comedication or other nongenetic factors and is quite common.[14]Phenoconversion is a complex phenomenon that leads to genotype–phenotype Mismatching without any genetic abnormality. It is particularly well-characterized for cytochromes P450 2D6 and 2C19. Although transient, phenoconversion can have a significant Impact on the analysis and interpretation of genotype-focused clinical outcome correlations and in forensic toxicology conclusions.[15]but, also, in everyday clinical practice. Phenoconversion resulting from nongenetic extrinsic factors has a significant impact on The analysis and interpretation of genotype-focused clinical outcome association studies And, ultimately, to the personalization of therapy in routine clinical practice. Having the Genotype data available can help identify those nongenetic factors, which may lead to a Decreased risk for the patient to suffer from adverse drug reactions by following a different Treatment algorithm (e.g., order TDM, treat the infection, avoid the drug interaction, etc).Examples of nongenetic factors include inflammation, cancer, age, liver disease, and renal Dysfunction .[16]

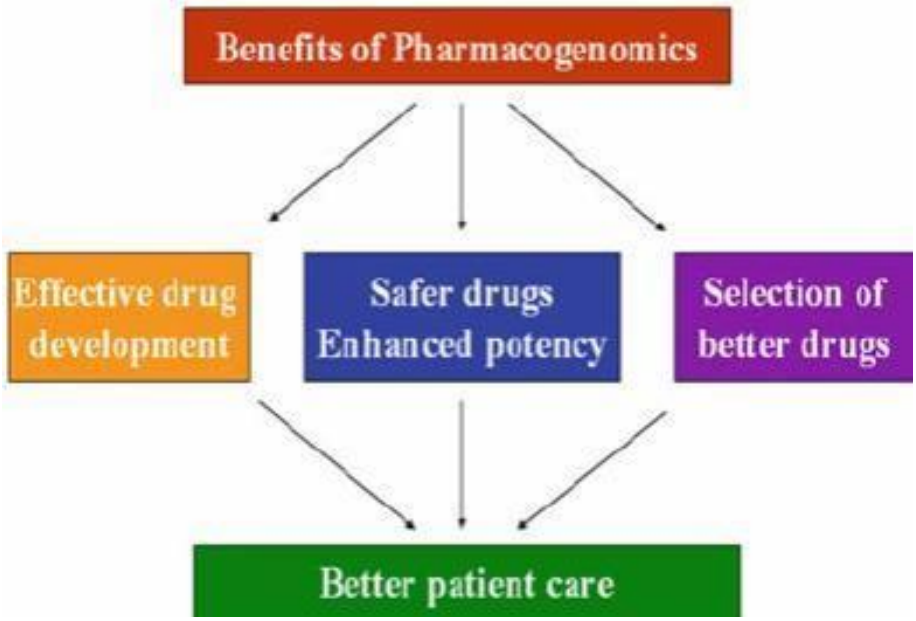

Fig 4. Benefits of Pharmacogenomics

Pharmacogenetics of Systemic Breast Cancer Treatment

Systemic treatments for breast cancer Are divided into hormonal interventions, chemotherapy, and novel Agents. Antitumor activity or safety of Specific agents may depend not only On drug dose and schedule but also on Functional targets, drug metabolizing Enzymes, and transporters. Some Agents are prodrugs with one or more Metabolites that may contribute to the Drug's antitumor activity or to specific Sideeffects. Prospective determination Of genetic variants in drug metabolizing enzymes or drug transporters Could be used to determine likelihood Of response and/or propensity to adverse effects. Response to a specific Agent may also depend on variants in The target of the treatment. It is

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Possible that small genetic variations In the target mayaffect the response of Toxicity related to the agent. In this Review we will focus on the current Knowledge of the role of pharmacogenetics in predicting efficacy and safety Of standard and emerging breast cancer treatments

HORMONALTHERAPY

More than 50% of primary breast Cancers will express the estrogen receptor (ER)and/or progesterone receptor (PgR). Almost every woman with Hormone receptor- positive disease will Be offered some form of hormona Intervention to treat the cancer. Most Women with earlybreast cancerwill Likelyreceive adjuvant tamoxifenfor5 Years. Postmenopausal women may be Offered aromatase inhibitors instead of Or following tamoxifen, and premenopausal women may undergo ovarian Suppression instead of or with tamoxifen. Tamoxifen has also been approved to reduce the incidence of a New breast cancer in women at high

Pharmacogenetics of Anticencerdrugs

1) Tamoxifen

A common treatment for hormone-dependent breast cancer. The effectiveness of tamoxifen depends on the patient's ability to convert it to endoxifen, an activemetabolite. Genetic variations in the CYP2D6 and CYP2C19 genes can affect this process.

5-Fluorouracil(5-FU)

An antimetabolite chemotherapy drug that affects DNAsynthesis. Polymorphisms in the DPD gene can affect how a patient responds to 5-FU.

Trastuzumab

A targeted therapy drug. Genetic polymorphisms in the HER2 gene can affect how a patient responds to trastuzumab.While there are many studies on pharmacogenomics and breast cancer, there are still challenges to using these studies in clinical practice. These challenges include how to interpret the results and whether to use pharmacogenetic tests in the clinic. Future efforts include integrating pharmacogenomic data into clinical practice, improving real-time treatment monitoring, and ensuring equitable access to genetic testing of Systemic Breast Cancer treatment

Genetics Factors Influencing the drug Response

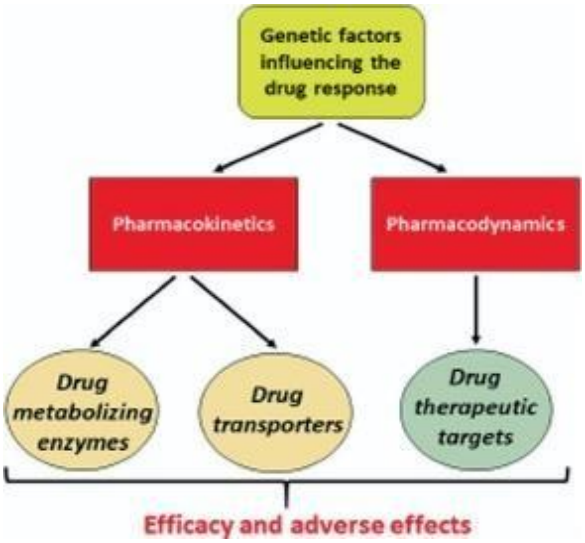

Fig 5. Genetics Factors Influencing the drug Response

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Pharmacogenetic Studies of Anti-Diabetes Drugs

1) Sulfonylureas

1. Background

Sulfonylureasareone of themost widelyused classesof oralhypoglycemicagents. The most Common sulfonylurea agents are tolbutamide, gliclazide, glibenclamide, and glimepiride, and while Most individuals respond well to these drugs, pharmacodynamic responseefficacyisvariable.ForExample,10-20%oftreatedindividualsdonotachieve adequate glycemic control using even the Highest recommended dose ("primary sulfonylurea failure") and 5-10% of patients with T2D who Initially respond to sulfonylurea treatment will subsequently lose the ability to maintain near-normal Glycemic levels ("secondary sulfonylurea failure") [17]. Further, drug dosages typically need to be Increased over time as impairment of insulin secretion occurs, until a second hypoglycemic agent is Added or, if all hypoglycemic drugs fail, adding or switching to insulin is indicated. Although failure to Respond, or deterioration of, response to sulfonylurea therapy is known to result from a variety of Factors including poor dietary and/or physical activity compliance, weight gain, reduction of insulin Sensitivity, age of onset, or presence of anti-islet cell and glutamic acid decarboxylase antibodies, the Strongest predictor of failure is deterioration of β-cell function.[18]

Maturity-onset diabetes of the young (MODY) is a rare, autosomal dominant formof diabetes. There Are six primary forms of MODY, each a consequence of mutations in six different genes [28]. In addition To the autosomal dominant inheritance, MODY is characterized by onset before the age of 25 and β-cell Dysfunction typically in the absence of insulin resistance or obesity. MODY3 arises from mutations in The hepatocyte nuclear factor 1 homeobox A gene (HNF1A), and patients with this disease are Hyper-sensitive to the hypoglycemic effects of sulfonylureas [14]. In an early case study, Pearson et al.[30] identified three MODY3 patients with HNF1A mutations, in whom cessationand reintroduction of Sulfonylureas caused dramatic changes inHbA1c levels, or severe hypoglycemia, in response to Introduction of sulfonylureas into the treatment regimen. A subsequent study found that MODY3 Patients had a 5.2-fold or 3.9-fold greater response to gliclazide compared to metformin or patients With T2D, respectively [19]. These patients also had a stronger insulin secretory response to Tolbutamide and weremore insulin-sensitive comparedto individualswith commonT2D 20

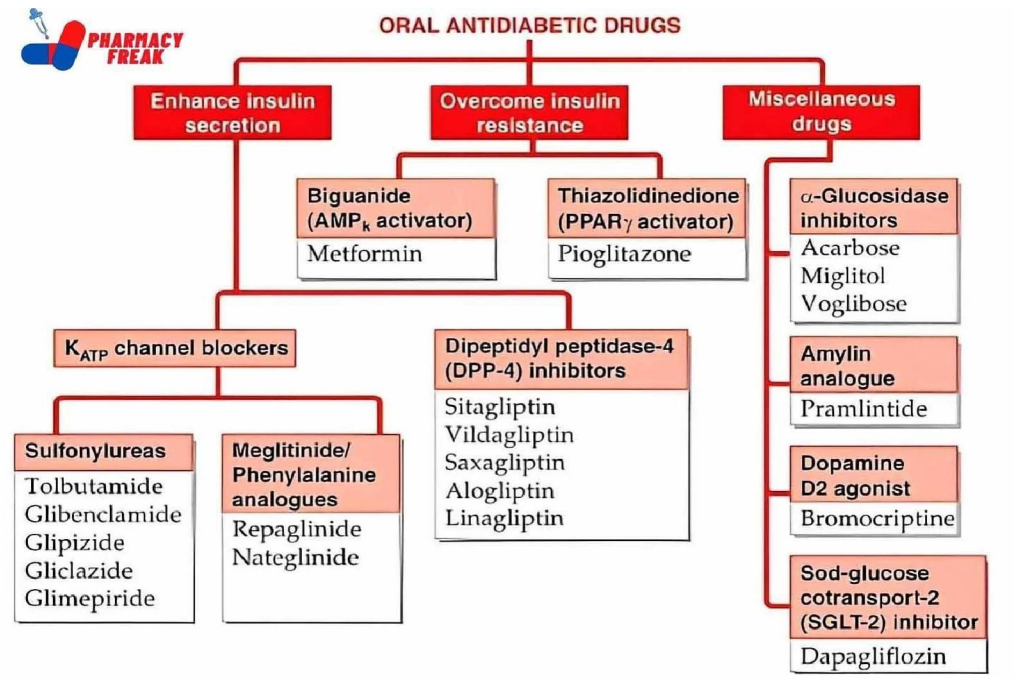

Fig 6. Oral Antidiabetic drugs

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Sulfonylureas stimulate insulin release from pancreatic β-cells by first binding to thehigh affinity Plasma membrane receptor (SUR1) coupled to an ATP-dependent K+ channel (KATP). This interaction Closes the K+ channel, which inhibits potassium efflux and depolarizes the plasma membrane, leading To an opening of voltage-gated calcium channels.

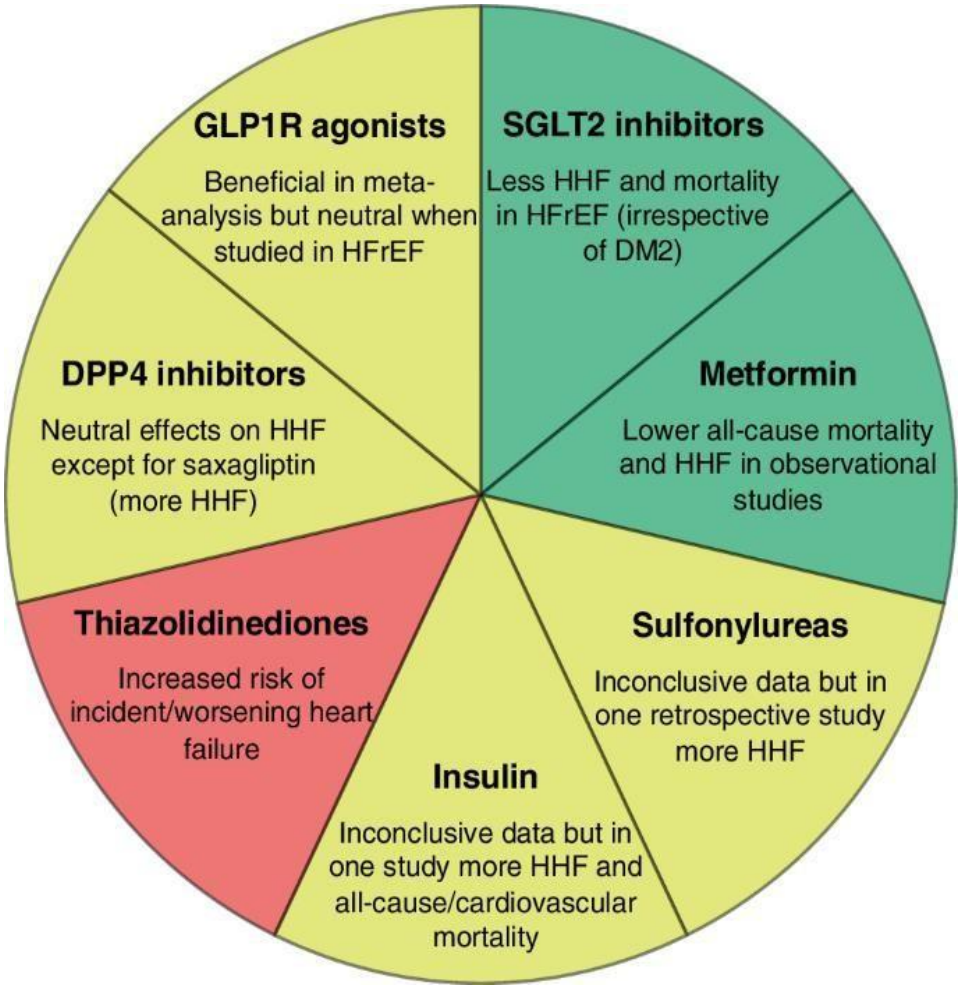

Fig 7. The effect of Antidiabetic agents on heart failure

IV. CONCLUSIONS

Pharmacogenetics research provides a means to better understand and improve on pharmacotherapy. However, pharmacogenetic studies of T2D the rapieslag behind those for other complex diseases, Despite the fact that pharmacologic interventions for T2D have been studied extensively at both the Clinical and epidemiologic levels. Among the studies that have been conducted, several have identified Variants that are potentially associated with differential response to anti-diabetes medications; these Preliminary results are promising and warrant investigations in larger, well-designed cohorts to assess Their potential roles in optimal drug selection and individualized pharmacotherapy in patients with T2D. At this time, larger, well-powered studies with clearly defined outcomes and utilizing a global Approach are needed, as they will not only be more informative than extant candidate gene Investigations, but will also be necessary to define the array of genetic variants that may underlie drug Response.Such results will likely enable achievement of optimal glucose control, improvement of Therapeutic efficacy, and reduction in risk of adverse drug events in at-risk patients, which together Will lead to personalized treatment strategies for all individuals with T2D

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