Prehumble

- No Conflict of Interest
- Organisers of this meeting did not restrict me in any way in my slides neither they provided any,
- My stay and travel is sponsored by Intas Pharma,
- 14th February…..talking about the combination … particularly … on

Discussion points

- Type 2 Diabetes – Facts and figures
  - Situation in Nepal
  - Unmet needs
- Combination therapy in Type 2 Diabetes
  - Step care approach
  - Dual Combination
  - Triple combination
- Split Dose Vs Fixed dose combination
- Summary and Take Home message

Diabetes – Approx. 382 million people worldwide (IDF 2013)
Type 2 Diabetes Mellitus

- Diabetes epidemic is rapidly rising all over the globe at an alarming rate.
- Increment for both
  - The prevalence of type 1 diabetes is increasing also but
  - The major driver of the diabetes epidemic is type 2 diabetes, which accounts for more than 90 percent of all diabetes cases.
- Over the past 30 yr, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth & middle aged people.

Natural History of Type 2 Diabetes

- Relative Insulin Deficiency
- Post Meal Glucose
- Fasting Glucose
- Insulin Resistance
- Insulin Level

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Diabetes Mellitus: Nepal (IDF Atlas)

- Population of Nepal (aged 20-75 yrs) is 1.49 cr in 2013.
- Prevalence of Diabetes mellitus in Nepal is increasing,
- Death attributable to diabetes mellitus are 14,531.
**Diabetes Update**

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**Unmet Need in Type 2 Diabetes**

- Multiple defects in type 2 diabetes
- Insulin resistance
- Type 2 diabetes
- Hyperglycaemia
- Adverse effects of therapy
- Weight management
- CVD Risk (Ischaemia and Hypertension Control)

**To me --- most important**

1. Early Diagnosis,
2. Good HbA1C.

**Most Patients with T2DM Do Not Achieve HbA1c Goals**

<table>
<thead>
<tr>
<th>Therapy used</th>
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**% of Patients With Diabetes Having A1C <7%**

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**Our data – Manipal Hospital, Bangalore**

- N=334
- HbA1c
  - < 7% in 39%, > 13% in 10%
  - 8% had retinopathy
  - Nephropathy
    - 33% microalbuminuria
    - 4% Creatinine value of >1.6 mg/dl
    - 6% CAD
    - 31% had Dyslipidaemia
    - Hypertension

**Summary and Take Home message**

- Early Diagnosis
- Good HbA1C
Manipal Hospital In-patient Survey.
HbA1C: <7 %, 7-8 %, >8 - 78 %.

HbA1C in hospital, Hope Hospital, Manchester.
Done in 52: <7 - 25%, 7-8 - 35%, >8 - 40%.
Bhattacharyya A et al, Diabetic Medicine 2001

Manipal Hospital Analogue Survey n = 244
Average HbA1C - 9.1 +/- 2.1

Diabetic Medicine 2001
Manipal Bio Lab, n = 676, July 2010.
HbA1C <7 %, 7-8 %, >8 - 52 %.

Unpublished.

**Our data – MHB**

**Real world**

**Approach to Management of Hyperglycemia: ADA 2014**

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**Biguanides: Metformin**

- From consensus of all available guidelines,
  - Metformin is the 1st line agent for treatment of T2DM.
  - Many important Features of Metformin
- But due to progressive nature of type 2 diabetes mellitus, metformin monotherapy will not be eventually sufficient for majority of patients.

**...... the Valentine Day ......**

- Valentine’s Day is said to take its origin from 3rd century Rome as a tribute to St. Valentine, a Catholic bishop
- Roman Emperor Claudius banned marriage from his empire. But Valentine secretly performed marriages. When Claudius found out about Valentine, he sentenced him to death.
- While in prison, Valentine fell in love with the blind daughter of his jailer. Before his death, he sent a farewell message to her, signed "From your Valentine." This phrase is still used today.
**Discussion points**

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**Available options for Combination Therapy in T2DM**

- There is a definite need for ideal 2nd line agent where metformin is not sufficient to achieve glycaemic control.
- Available options for 2nd Line agent after metformin monotherapy are:
  - Sulfonylureas
  - DPP-4 Inhibitors
  - Thiazolidinediones
  - α-Glucosidase Inhibitors
  - GLP-1 Agonist
  - Insulin

**Sulfonylureas**

- First Generation
  - Tolbutamide
  - Chlorpropamide
  - Acetohexamide
- Second Generation
  - Glyburide
  - Glipizide
  - Gliclazide
  - Glimepiride

**Biguanides: Metformin**

- Advantages
  - No weight gain
  - No hypoglycemia
  - Long record of safety
  - Decreased macrovascular complications
  - Prevents diabetes
  - Malignancies
- Disadvantages
  - Heart Failure
  - Renal disease
  - Liver dysfunction
  - GI side effects

- 1. Increased risk of hypoglycemia
- 2. Metformin & lactic acidosis
  - US: stop @SCr ≥ 1.5 (1.4 women)
  - UK: dose @GFR <45 & stop @GFR <30

**Sulfonylureas**

- Advantages
  - Once daily dosing, mostly
  - Immediate benefits
  - Well-tolerated
  - Inexpensive
- Disadvantages
  - Hypoglycemia
  - Weight gain
  - Caution –
    - Hepatic Dysfunction
    - Renal dysfunction
**Effects on cardiovascular outcomes**

- All sulfonylureas carry an FDA warning about the increased risk of CV death
- Experimentally, sulfonylureas (Glibenclamide & Tolbutamide) that bind to myocardial KATP channels have been shown to block the beneficial effects of ischemic preconditioning
- Gliclazide or Glimepiride, are exclusively pancreatic beta-cell specific and might offer advantages over older agents.

**Ischaemic Preconditioning**

Repeated and brief occlusion of the same vessel conditions the myocardium such that subsequent prolonged occlusion leads to a smaller infarct (ischemic preconditioning).

**K\(_{ATP}\) Channel Complex**

Some sulfonylureas are not selective for heart or pancreas K\(_{ATP}\) channels.

The K\(_{ATP}\) channel, a complex of a sulfonylurea receptor (SUR2A, SUR1) and the potassium channel (Kir6.2) is key to glucose-mediated insulin release from pancreatic β-cells.

**Glimepiride & Cardio safety**

- The Risk of overall Mortality in Patients With Type 2 Diabetes Receiving Glipizide (n=4,279), Glyburide (n=4,325), or Glimepiride (n=2,537) Monotherapy showed that:
  - Overall mortality risk in those with documented CAD: Glyburide vs Glimepiride (HR - 1.36) Glipizide vs Glimepiride (HR - 1.39) [0.99 –1.96])
  - Glimepiride is the preferred SU for those with DM & CAD.

**Sulfonylurea + Metformin**

- Considering all the available evidence, it seems that the newer generation sulfonylures like Glimepiride is suitable agent as add-on therapy to metformin.
  - Less risk of Hypoglycemia
  - Less/No Weight Gain
  - Cardio safety
  - Low Cost
  - Huge Clinical & Real-life practice Experience

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**Valentine's Day**

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- The phrase is still used today.
Thiazolidinediones

Pioglitazone & Rosiglitazone

- Act by stimulating PPARγ, a member of nuclear receptor superfamily
- Increase insulin action at muscle (liver)

Advantages
- Less hypoglycemia
- Can be used in patients with mild renal failure
- Improve TG & HDL-C
- Prevents diabetes
- Improves beta cell mass

Disadvantages
- Weight gain
- Oedema
- Increases LDL
- Delayed onset of action
- Fracture risk, Ca bladder etc

Thiazolidinediones

TZDs plus Metformin

- Thiazolidinediones are also a good option as add-on therapy to metformin, i.e., Pioglitazone
- Important points to consider when selecting Pioglitazone as add-on
  - Weight Gain
  - Risk of Heart Failure
  - Risk of Bladder Cancer
  - Reduction in Bone Mineral Density
  - Very low risk of Hypoglycemia
  - Low Cost of therapy
DPP-4 Inhibitors plus Metformin

- DPP-4 Inhibitors are newer antihyperglycaemic therapies in management of T2DM.
- Examples:
  - Sitagliptin
  - Saxagliptin
  - Linagliptin
  - Alogliptin
  - Vildagliptin etc.

Drugs acting on Incretin Axis

**Advantages**
- Once daily dosing
- Hypoglycemia less
- Weight neutral/loss
- Can be used in renal impairment

**Disadvantages**
- CV safety nearly proven
- Expensive
- Side effect profile

DPP-4 Inhibitors plus Metformin

- DPP-4 Inhibitors are a highly considerable option as 2nd line agent to metformin in case of inadequate glycaemic control.
- High cost of therapy is the only burning issue related to DPP-4 inhibitors due to various reasons:
  - Chronicity of treatment,
  - Cost associated with comorbid conditions to T2DM like Hypertension, Dyslipidemia etc.
  - Economical condition of majority of patients in developing countries

α - Glucosidase Inhibitors (AGIs) plus Metformin

- AGIs are also safe & effective add-on therapy option in T2DM.
  - Example: Acarbose, Voglibose, Miglitol
- There are important points consider with usage of AGI as add-on therapy
  - Gastrointestinal Adverse Events
  - Modest Glycemic Control
  - Very low risk of Hypoglycemia
  - Weight Neutral/Weight Loss
  - Low Cost of therapy

Second OHA added to Metformin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hypo</th>
<th>Glimepiride</th>
<th>Piozone</th>
<th>Glipitin</th>
<th>Acarbose</th>
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<tr>
<td>Piozone</td>
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Hypoglycemia Possible
In the second half of the 20th century, the practice of giving gifts along with paper-laced cards became popular. Roses, candies and chocolates are the most commonly exchanged Valentine’s Day Gifts. Today, it is estimated that one billion Valentine cards are sent each year, 85% of which are sent by women.

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Triple Combination Therapy
- In case of inadequate glycaemic control, triple combination therapy need to be considered.
- The available options are:
  - Metformin + SU + TZD
  - Metformin + SU + DPP-4 Inhibitor
  - Metformin + SU + AGI
  - Metformin + DPP-4 inhibitor + TZD
  - Metformin + DPP-4 inhibitor + AGI

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Split Dose Vs Fixed dose combination
- Simpler dosage schedule improves compliance and treatment outcomes.
- Allows for synergistic combinations Less expensive than single ingredient drugs.
- Pharmacokinetics difficult because of different elimination half lives of individual component.
- Drug interactions may lead to alteration of the therapeutic effect.
- If a patient is allergic or has a side-effect to 1 component, the FDC must be stopped and replaced by separate tablets.
- Potential quality problems, requiring bio-availability testing.
Compliance

<table>
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<tr>
<th>Number of Medication Component titration Flexibility</th>
<th>Split dose</th>
<th>Fixed dose</th>
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</thead>
<tbody>
<tr>
<td>Medication Error</td>
<td>Less</td>
<td>Less</td>
</tr>
<tr>
<td>Cost</td>
<td>Better</td>
<td>Lesser</td>
</tr>
<tr>
<td>Component titration</td>
<td>Possible</td>
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**Summary and Take Home message**

- T2DM is a growing epidemic all over the world leading to a heavy burden of micro & macrovascular complications,
- Due to progressive nature, there is definite need of add-on therapy to Metformin for better glycaemic control,
- SU (specially newer generation SU like Glimiperide), DPP-4 Inhibitors, TZDs & AGIs are all good options,
- In total, Metformin with Glimiperide looks the best option.

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**In Conclusion...**

- **Screening and Detecting**
  Diabetes early is important,
- **Combination therapy** should be considered early for better control,
- **HbA1C** target has to be individualized,
- Overall comprehensive Treatment is the _key to success_.

www.DiabetesEndocrinology.in

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**Jai Ho**