TIGAR™ Report Advisory Notes

GENERAL

IR2Dx TIGAR™ is meant for use with adult Type 2 diabetes patients.

- Data on Type 1 patients and children with Type 2 diabetes is limited, and is an insufficient basis for TIGAR's analysis and reporting. Use of TIGAR™ with these categories of patients is not supported by IR2Dx.

CARDIOVASCULAR DISEASE / HEART FAILURE

Ejection Fraction Measurements

Patients diagnosed with diabetes have a high risk of cardiovascular disease. Clinical evaluation, including history and symptoms of cardiovascular disease should be performed. If the patient seems to have a risk of significant heart failure, heart condition should be assessed using routine tests and procedures such as an ECG, BNP hormone measurement, or echocardiogram. A low ejection fraction (EF), can be a sign of heart failure. Although there is left ventricular EF and right ventricular EF, in most cases the term "ejection fraction" refers to left ventricular ejection fraction.

Ejection fraction can be measured using:

- Echocardiogram (echo) - this is the most common way to check EF
- Magnetic-resonance-imaging (MRI) - scan of the heart
- Nuclear medicine scan of the heart using multiple gated acquisition (MUGA); also called a nuclear stress test

According to the Cleveland Clinic website:
Normal ejection fraction is 55% to 70%
Slightly below normal is 40% to 54%
Moderately below normal is 35% - 39%
Severely below normal is <35%

Ejection Fraction Adjustments

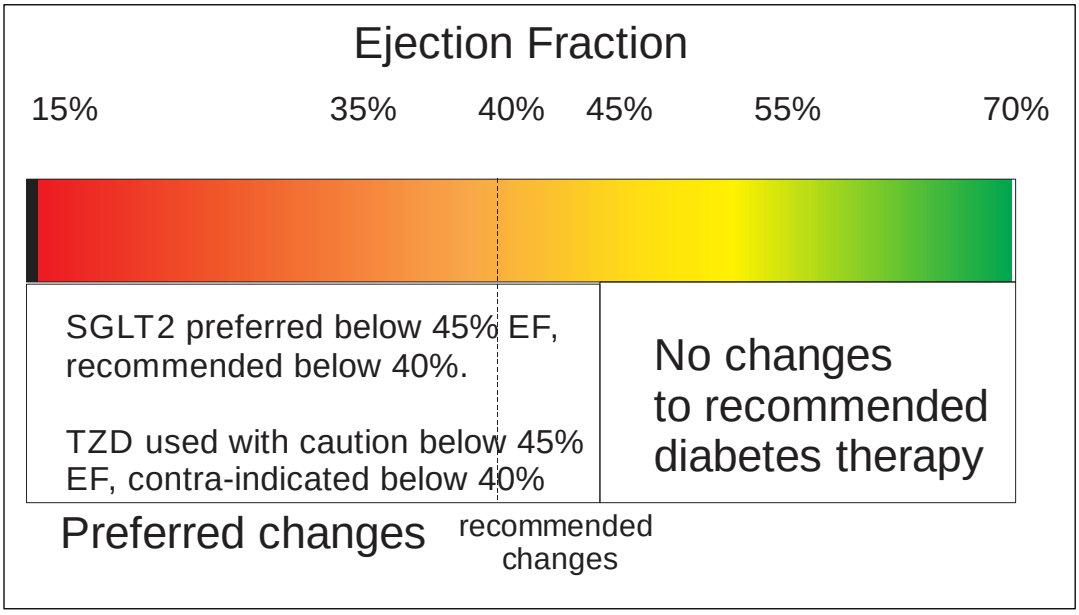
Our advisors believe clinicians need to consider heart failure status when relevant, and if heart failure is present, the degree of impaired function as indicated by the EF, when choosing the anti-diabetic drug class to be used.
When EF is more than 45% there is no need to consider a change from the Recommended Drugs in the TIGAR report. When EF is below 45%, the physician should start considering changes and adjustments. Among the major drug classes, one is preferred in significant

1. All references can be found in the" TIGAR Report References" document

heart failure (SGLT-2i), and one is contra-indicated (TZD). The remaining major classes are neutral with respect to heart failure.

Below an EF of 40%, there are definite suggested changes to the use of the SGLT-2i s and TZDs, particularly pioglitazone.

- If the EF is 45% or below, an SGLT-2i is preferred as drug of choice, with the best clinical study data having been demonstrated for empagliflozin and dapagliflozin.
- If the EF is 40% or below, an SGLT-2i is strongly preferred as a drug of choice as compared with other anti-diabetic drug classes. TIGAR recommendations may suggest that other drugs also will be required to improve glucose control, metabolic pathway function, and reduce overall risk profiles.
- TZDs, and particularly Pioglitazone, are contra-indicated when the EF is below 40%, and should be used very cautiously when the EF is between 40 – 45%. TZDs may be used when recommended if the EF is 45% and above. The patient on TZDs should be monitored for changes in condition, particularly signs of worsening heart health, including edema.



- **Prediabetes:** At this time, no anti-diabetic drug class has specific FDA approval for use in prediabetes populations. Only metformin, pioglitazone (a Thiazolidinedione) and liraglutide (a GLP-1 analog) have published data in prediabetes patients. Liraglutide 3.0 mg (Saxenda®), a higher dose GLP-1 subcutaneous injection, has been approved for weight loss by the FDA. Use of all anti-diabetic drugs in pre-diabetes patients must be subject to physician judgment, given the lack of positive proof of effectiveness, whether based on the published data, patient test results, matches of biochemistry and drug mode of action, or action on insulin resistance. Physician judgment should also be applied to any drug data developed from patients in later stages of disease, or any other factors.

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- **Diabetes related costs:** treatment optimization may reduce overall ongoing medical costs for patients, even in the first year thereafter, despite higher diabetes drug costs. [42]. Other studies indicate that reduced cardiovascular event rates can be achieved in the intermediate term, providing further savings. Long term costs savings due to fewer complications are thought to be significant, and may become better defined through additional studies.

MARKERS: HbA1c

HbA1c Testing

- The accuracy of the HbA1c test has recently been improved by the National Glycohemoglobin Standardization Program (NGSP). However, the variation in the test results can be as high as +/- 0.5%. Health care providers can find information regarding the accuracy of the HbA1c test used by their laboratory at www.ngsp.org. The averaging of glucose levels over the 3- month life cycle of red blood cells avoids the natural variability of daily glucose measurements. However, the test tends to reflect the last 30 days of glucose levels and may disguise a problem in glucose management during the first 30 days after a HbA1c measurement. Although HbA1c remains the 'gold standard' for blood glucose control, the test may not provide a complete estimate of the clinical complications of diabetes.
- Other clinical conditions which may significantly change the apparent HbA1c results are hemoglobin disorders, including sickle cell anemia or thalassemia. The NGSP provides information about which HbA1c tests are appropriate to use for specific hemoglobin variants at www.ngsp.org.

Further information can be found in the following:

1. Consensus statement on worldwide standardization of the hemoglobin A1c measurement: American Diabetes Association, European Association for the Study of Diabetes, International Federation of Clinical Chemistry and Laboratory Medicine and the International Diabetes Federation. Diabetes Care 2007; 30:2399-2400.

2. International Expert Committee Report on the Role of the A1c Assay in the Diagnosis of Diabetes. The International Expert Committee. Corresponding author: David M. Nathan. The International Expert Committee Diabetes Care 2009 32(7) 1327-1334.

3. Flat-Sugar: Benefit of Reducing Glycemic Variability in Diabetes? Medscape Jun 17, 2015.

4. Relationship between glycated hemoglobin levels and mean glucose levels over time. Nathan DM, Turgeon H, Regan S. Diabetologia 2007; 50:2239-2244.

1. All references can be found in the" TIGAR Report References" document

5. Pitfalls in Hemoglobin A1c Measurement: When Results may be Misleading. Michael S. Radin. J Gen Intern Med 2014 Feb; 29(2): 388-394.

MARKERS: hsCRP

- If hsCRP is >10 ug/ml rerun the test at least two weeks later. A result greater than 10 could indicate acute infection.

hsCRP - in diabetes patients

- Statins lower hsCRP levels, a well-recognized biomarker for inflammation associated with risk of cardiovascular events and diabetes. TZD's have demonstrated additive benefit in combination with selected statins in patients, with and without diabetes, and with cardiovascular risk [1][7][8][20][44][49][50][51][52][59].[1]
- GLP-1 antagonists alone lower hsCRP levels, cholesterol and intima media thickness in Type 2 diabetes patients [9] [61].

hsCRP - in prediabetes patients

- Statins have demonstrated slight increases in the incidence of diabetes onset, with an increased hazard ratio usually in a range from less than 10% to 22% (< 1.1 – 1.22). However, the risk was much higher in one large study [54] with a hazard ratio of 1.46 [95% D.I. 1.22-1.74]. Concerns regarding increases in fasting glucose and risk of diabetes associated with the use of statins should be weighed against their well-established benefits in reducing cardiovascular risk, including in patients where a high hsCRP level is the only risk factor [49][51][53].
- There are no studies in prediabetes patients specifically designed to lower cardiovascular risk using a GLP-1 plus a statin. However, studies have shown that using a GLP-1 alone will lower hsCRP levels, cholesterol and intima media thickness in Type 2 diabetes patients. This is an important area for further research [9][61].
- IR2Dx has several studies in prediabetes patients that demonstrated synergy in lowering cardiovascular risk with pioglitazone alone and in combination with two different statins, as measured by hsCRP, and other major surrogates like HDL, intima media-thickness of the arterial walls, triglycerides and other markers of cardiovascular risk. In addition, a long-term study in high risk prior stroke or TIA patients, published in 2016, demonstrated a statistically significant reduction in CV events in the prediabetic patients who received pioglitazone vs. those on placebo. [20][33][34][58][66]

DRUG CLASSES:
Pioglitizone/TZDs

- Numerous studies on bladder cancer risk in TZDs have yielded clear results for rosiglitazone, and inconsistent results for pioglitazone. Results of studies of rosiglitazone varied very little despite a variety of sizes and designs, collectively indicating no increased risk for bladder

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cancer associated with this drug. In contrast to this, the results of studies assessing the bladder cancer risk associated with the use of pioglitazone have been inconsistent, though the great majority did not demonstrate increased risk. The biggest (over 1,000,000 patients in 6 populations) and longest (a ten year follow up study at Kaiser) did not show increased risk. Two studies, each in single population databases in the U. K. and France, showed elevated risk for bladder cancer associated with use of pioglitazone. Other studies have had mixed results, though most do not show risk. The US FDA has ongoing safety evaluation underway and recommends that patients with active or a prior history of, bladder cancer not receive pioglitazone [55].

Metformin

- The long-term use of metformin has been linked to higher incidence of vitamin B-12 deficiency. Additionally, those with B-12 levels below 250 pmol/l had lower cognitive outcomes. Regular monitoring for vitamin B12 deficiency, and if necessary treatment of such patients, is recommended [36]. A blood level should be used for initial testing, and if it is low, a radioactive B12 absorption test is warranted to determine if the patient has difficulty absorbing it. Depending on the nature of the deficiency, pills or injections may be necessary.

SGLT-2 Inhibitors

Cardiovascular Effects and Heart Failure:

- One SGLT-2 inhibitor, Jardiance® (empagliflozin), demonstrated significantly lower rates of death from cardiovascular causes, hospitalization for heart failure and death from any cause, compared with placebo, in a large outcome trial presented in 2015. The primary driver of these results were improvements in patient outcomes related to heart failure [38].
- Confirmatory studies with a second SGLT-2 inhibitor, Invokana™ (canagliflozin) also showed reductions in CV risk. See package inserts for statistics and details in CV risk. A third drug will have their results published in 2019, as will a fourth compound that is not yet FDA approved.
- Recent data from a large (364,828 patients) multi-country study shows apparent class benefits of SGLT-2 inhibitors when compared to other anti-diabetic medications in reducing risk of hospitalization for heart failure (HR. 0.61; $p < 0.0001$) and all-cause deaths (HR. 0.49; $p < 0.0001$) [64]. This provides evidence of a class effect.

Kidney Function Limitations:

- Assess renal function before initiating SGLT-2i medications
- Do not initiate Farxiga™ if eGFR is below 60mL/min/1.73m2
- Do not initiate Invokana™ if eGFR falls persistently below 45mL/min/1.72m2. Dose can be increased to highest dose in patients tolerating the 100 mg dose with eGFR>60 mL/min/1.72m2

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- Jardiance™ should not be initiated in patients with an eGFR < 45 ml/min/1.73m2.
- In addition to reductions in CV and all-cause deaths and hospitalizations for heart failure, compared with placebo empagliflozin (Jardiance™) and canagliflozin (Invokana™) both demonstrated consistent statistically significant reductions in decreases of eGFR and in disease progression to severe renal dysfunction. Ongoing trials may provide new information as to whether the improved kidney function is a class effect.

Amputation risk with Invokana™ (canagliflozin): Invokana™ has a new FDA black box warning regarding increased risk of toe amputations compared to placebo from their large canagliflozin outcome trial (CANVAS). The canagliflozin study arm revealed a higher risk of lower limb amputations compared to placebo - HR 1.97, 6.3 vs. 3.4/1000 patient-years. See package insert to review FDA warning.

Ketoacidosis: A 415,670 patient Danish study that looked at over 3,000,000 person years found no significant difference in rates of ketoacidosis between SGLT-2 inhibitors and other non-insulin glucose lowering drug classes. The absolute level of risk is approximately 1 per 1,000 patient/years, so this is a very rare condition. It usually occurs in patients on insulin. [See Manufacturer's package insert or FDA for more information]

DPP-4 Inhibitors

- Of the four DPP-4 inhibitors approved by the FDA not including combination medications, only three have completed required post-market outcome studies and all three met the FDA criteria of less than 30% increased risk of cardiovascular disease. However, there are differences in the hazard ratios of these three medications, with only one of the three Januvia™ (sitagliptin) showing no increased CV risk compared to placebo.
- There are currently 12 DPP-4 inhibitors available in selected International markets, some only available in Japan or South Korea. There is one additional product available in Europe, vildagliptin, plus the four mentioned above that are available in the US and Europe.

Sulfonylureas

- A minority of patients will do well with Sulfonylureas, which raise insulin secretion, and help to control glucose. However, in many clinical situations, sulfonylureas are NOT RECOMMENDED, as they are not optimal. They particularly should be used with caution in patients with cardiovascular disease and the elderly, and have numerous disadvantages as follows:
    - Cause hypoglycemia requiring blood glucose monitoring
    - Increased risk of hypoglycemia with concomitant insulin use
    - Do not address insulin resistance or cardiovascular disease
    - Increased risk of hip and other fractures [43]
    - More potent in renal impairment, with an additional increase in the risk of hypoglycemia

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- Should not be used in severe renal failure

GLP-1 Inhibitors

- Avoid in severe renal failure [14]. However, Trulicity (dulaglutide) has a broader indication in impairment, and is not contraindicated in patients with impaired renal function, including end stage renal disease (ESRD). Moderately to severe renal impaired patients should be carefully monitored including for symptoms of adverse GI side effects.

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