EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 12
Year: 2024

# EFFICACY AND SAFETY OF DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS IN TYPE 2 DIABETES A CRITICAL REVIEW OF CARDIOVASCULAR AND ONCOLOGICAL OUTCOMES

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**Article Received on 01/10/2024** **Article Revised on 21/10/2024** **Article Accepted on 10/11/2024**

**ABSTRACT**

Dipeptidyl peptidase-4 (DPP-4) inhibitors represent a significant advancement in managing type 2 diabetes mellitus (T2DM). This review systematically examines their efficacy and safety, focusing on cardiovascular outcomes and cancer risks. Our analysis, based on major clinical trials and observational studies, reveals that DPP-4 inhibitors effectively reduce glycated hemoglobin levels and maintain a favorable safety profile. While cardiovascular outcomes show general neutrality, heart failure risk has emerged as a consideration with specific agents. Oncological safety data remains reassuring, though long-term surveillance is ongoing. This review provides critical insights for clinicians managing diverse T2DM patient populations, particularly elderly patients with multiple comorbidities.

**KEYWORDS**: DPP-4 inhibitors, type 2 diabetes, cardiovascular outcomes, cancer risk, glycemic control, elderly patients.

## 1. INTRODUCTION

### 1.1 BACKGROUND

The global prevalence of type 2 diabetes mellitus (T2DM) presents significant challenges for healthcare systems, increasing the demand for effective and safe therapeutic options. DPP-4 inhibitors have emerged as a valuable class of oral antidiabetic medications due to their unique efficacy in glycemic control and low risk of hypoglycemia and weight gain. This review addresses the cardiovascular and oncological safety of DPP-4 inhibitors and their specific therapeutic role in managing elderly patients with T2DM.

### 1.2 RESEARCH QUESTION AND OBJECTIVES

This review addresses three critical questions

1. What is the current evidence regarding the cardiovascular safety profile of DPP-4 inhibitors?
2. How do these medications impact cancer risk in T2DM patients?
3. What are the specific considerations for elderly patients using DPP-4 inhibitors?

## 2. MATERIALS AND METHODS

### *2.1 Search Strategy*

We conducted a systematic review of the literature published up to 2023, utilizing databases including PubMed, MEDLINE, and Cochrane Library. Keywords used were "DPP-4 inhibitors," "type 2 diabetes," "cardiovascular outcomes," "cancer risk," and "elderly."

### *2.2 Inclusion Criteria*

- Randomized controlled trials (RCTs)
- Large-scale observational studies
- Meta-analyses
- English-language publications focusing on cardiovascular outcomes, cancer incidence, and elderly populations

**Literature Review and Thematic Organization**

**1. Glycemic Efficacy and Safety Profile of DPP-4 Inhibitors**

DPP-4 inhibitors, including sitagliptin, saxagliptin, and linagliptin, have shown significant efficacy in lowering glycated hemoglobin (HbA1c) levels, typically by about 0.5%–1.0%. Their safety profile is favorable, with a low incidence of hypoglycemia and weight neutrality, making them suitable for older adults.

***Critical Analysis*:** While most studies agree on the efficacy and tolerability of DPP-4 inhibitors, variations exist regarding specific population responses, which warrants further investigation.

**2. Cardiovascular Outcomes of DPP-4 Inhibitors**

Cardiovascular outcomes are critical given the elevated cardiovascular risk among T2DM patients. Major trials have contributed to understanding DPP-4 inhibitors' cardiovascular effects.

- **SAVOR-TIMI 53 (Saxagliptin)**: Demonstrated a minor increase in hospitalization for heart failure without a corresponding rise in major adverse cardiovascular events (MACE).
- **TECOS (Sitagliptin)**: Showed cardiovascular neutrality, with no increased MACE risk.
- **EXAMINE (Alogliptin)**: Indicated cardiovascular safety, though a slight trend toward increased heart failure risk was noted.

***Discussion of Trends and Gaps*:** While most DPP-4 inhibitors show cardiovascular neutrality, the increased risk of heart failure with saxagliptin remains a topic of debate. Further studies are needed to validate these findings, particularly in high-risk subpopulations.

***3. Oncological Outcomes and Cancer Risks Associated with DPP-4 Inhibitors***

1. **General Cancer Incidence**: Meta-analyses have shown no significant increase in overall cancer risk, with some suggesting a possible protective effect against colorectal cancer.
2. **Pancreatic Safety**: Concerns regarding pancreatic cancer and pancreatitis remain inconclusive, with recent long-term studies showing no substantial increase in risk. However, this topic remains actively researched to ensure patient safety.
3. **Thyroid Cancer**: No increased risk has been observed.
4. **Bladder Cancer**: No significant risk elevation associated with DPP-4 inhibitors.

***Theoretical Implications*:** The potential anti-inflammatory mechanisms of DPP-4 inhibitors may play a role in mitigating cancer risk, but further mechanistic studies are needed to establish these effects conclusively.

**4. Efficacy and Safety in Older Adults**

For older adults, DPP-4 inhibitors offer significant advantages due to their minimal hypoglycemia risk and overall tolerability. However, studies suggest variable efficacy based on factors like body mass index (BMI) and pre-existing cardiovascular conditions, underscoring the need for personalized treatment approaches.

***Meta-Analysis Findings***

Meta-analyses confirm the overall cardiovascular safety of DPP-4 inhibitors, with a neutral effect on myocardial infarction or stroke rates across the agents. However, heart failure risk varies slightly among specific inhibitors, highlighting the need for individualized patient care.

## ANALYSIS AND DISCUSSION

**1. Synthesizing Findings**: This review synthesizes findings across multiple studies, highlighting DPP-4 inhibitors' general efficacy in glycemic control and their cardiovascular neutrality. However, saxagliptin's heart failure association emphasizes the need for patient-specific considerations.

**2. Comparing and Contrasting Research Methodologies**: An analysis of methodologies reveals that RCTs and observational studies yield consistent findings on DPP-4 inhibitors' safety, though observational data may better capture long-term risks such as cancer. Methodological rigor varies across studies, and future reviews could benefit from more homogenous data sources.

**3. Theoretical Implications and Gaps**: While anti-inflammatory effects and potential reductions in colorectal cancer risk are promising, long-term studies are required to confirm these outcomes. Moreover, the heart failure risk associated with specific DPP-4 inhibitors, such as saxagliptin, necessitates further targeted research.

**Limitations of Current Evidence:** While current studies are extensive, there are limitations

- Long-term follow-up data are limited.
- Population heterogeneity affects the generalizability of results.
- Definitions of cardiovascular outcomes vary, leading to potential inconsistencies across studies.

## CONCLUSION

DPP-4 inhibitors demonstrate strong efficacy for managing T2DM, offering significant benefits with minimal hypoglycemia and weight neutrality. Although their cardiovascular profile is generally neutral, specific risks such as heart failure with saxagliptin highlight the need for careful patient selection. On the oncological front, these inhibitors do not appear to increase cancer risk, although ongoing research is required to validate long-term safety.

***Future Directions***: Further studies should focus on

1. **Long-Term Cardiovascular and Oncological Effects**: To solidify DPP-4 inhibitors' risk-benefit profile for extended use.
2. **Mechanistic Research on Heart Failure**: Particularly with saxagliptin, to establish causative or associative relationships.
3. **Patient-Centric Research**: Exploring individual factors (e.g., BMI, age, cardiovascular history) to optimize treatment plans for varied patient populations.

## ACKNOWLEDGMENTS

We acknowledge the contributions of researchers whose work informed this review and our institutional colleagues who supported the manuscript's preparation.

**REFERENCES**


1. Inzucchi, S.E., Bergenstal, R.M., Buse, J.B., et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach. *Diabetes Care*, 2015; 38(1): 140-149.
2. Sherman, R.E., Anderson, S.A., Dal Pan, G.J., et al. Real-world evidence - what is it and what can it tell us? *New England Journal of Medicine*, 2016; 375(23): 2293-2297.
3. Tunis, S.R., Stryer, D.B., Clancy, C.M. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*; 2003; 290(12): 1624-1632.
4. Saturni, S., Bellini, F., Braido, F., et al. Randomized controlled trials and real-life studies. *Pulmonary Pharmacology & Therapeutics*, 2014; 27(2): 129-138.
5. Buse, J.B., Rosenstock, J., Sesti, G., et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). *The Lancet*, 2009; 374(9683): 39-47.
6. Garber, A., Henry, R., Ratner, R., et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomized, 52-week, phase III, double-blind, parallel-treatment trial. *The Lancet*, 2009; 373(9662): 473-481.
7. Nauck, M., Frid, A., Hermansen, K., et al. Long-term efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. *Diabetes, Obesity and Metabolism*, 2013; 15(3): 204-212.
8. Wysham, C., Blevins, T., Arakaki, R., et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care*, 2014; 37(8): 2159-2167.
9. Dungan, K.M., Povedano, S.T., Forst, T., et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomized, open-label, phase 3, non-inferiority trial. *The Lancet*, 2014; 384(9951): 1349-1357.
10. Weinstock, R.S., Guerci, B., Umpierrez, G., et al. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. *Diabetes, Obesity and Metabolism*, 2015; 17(9): 849-858.
11. Gerich, J.E. Contributions of insulin-resistance and insulin-secretory defects to the pathogenesis of type 2 diabetes mellitus. *Mayo Clin Proc*; 2003; 78: 447–456.
12. Creutzfeldt, W. The incretin concept today. *Diabetologia*, 1979; 16: 75–85.
13. Nauck, M.A., Bartels, E., Orskov, C., Ebert, R., & Creutzfeldt, W. Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7-36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. *J Clin Endocrinol Metab*, 1993; 76(4): 912–917.
14. Nauck, M.A., Meier, J.J. Incretin hormones: their role in health and disease. *Diabetes Obes Metab*, 2018; 20(Suppl 1): 5–21.
15. Nauck, M., Stöckmann, F., Ebert, R., & Creutzfeldt, W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*, 1986; 29: 46–52.
16. Nauck, M.A., Kleine, N., Orskov, C., Holst, J.J., Willms, B., & Creutzfeldt, W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*, 1993; 36: 741–744.
17. Drucker, D.J., & Nauck, M.A. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*, 2006; 368: 1696–1705.
18. Charbonnel, B., Dormandy, J., & Erdmann, E. The prospective pioglitazone clinical trial in macrovascular events (PROactive): Can pioglitazone reduce cardiovascular events in diabetes? *Diabetes Care*, 2004; 27: 1647–1653.
19. Dormandy, J.A., Charbonnel, B., & Eckland, D.J.A. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study. *The Lancet*, 2005; 366: 1279–1289.
20. Erdmann, E., Dormandy, J.A., & Charbonnel, B. The effect of pioglitazone on recurrent myocardial infarction in type 2 diabetes patients. *Journal of the American College of Cardiology*, 2007; 49: 1772–1780.
21. Wilcox, R., Bousser, M-G., & Betteridge, D.J. Effects of pioglitazone in type 2 diabetes patients with or without previous stroke. *Stroke*, 2007; 38: 865–873.
22. Dormandy, J., Bhattacharya, M., & Troostenburg, A-R. Safety and tolerability of pioglitazone in high-risk type 2 diabetes patients: Data overview from PROactive. *Drug Safety*, 2009; 32: 187–202.
23. Erdmann, E., Dormandy, J.A., Massi-Benedetti, M., Spanheimer, R. Pioglitazone and bladder cancer—Authors' reply. *The Lancet*, 2011; 378: 1544–1545.
24. Ali, M.K., Bullard, K.M., & Saaddine, J.B. Achievement of diabetes care goals in the U.S., 1999–2010. *New England Journal of Medicine*, 2013; 368: 1613–1624.
25. Scirica, B.M., Bhatt, D.L., & Braunwald, E. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *New England Journal of Medicine*, 2013; 369: 1317–1326.
26. Green, J.B., Bethel, M.A., & Armstrong, P.W. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine*, 2015; 373: 232–242.
27. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2

diabetes. *N Engl J Med;* 2015; 373: 2117–28. doi: 10.1056/NEJMoa1504720.

28. Pfeffer MA, Claggett B, Diaz R, et al.; ELIXA Investigators**.** Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med;* 2015; 373: 2247–57. doi: 10.1056/NEJMoa1509225.