

Pancreatic cancer and incretin therapy (GLP-1 and DPP-4)

Position Statement (Updated: July 2018)

Why have we produced this position statement

Some reports have linked the use of incretin therapy (GLP-1 and DPP-4) to increased risk of pancreatitis and pancreatic cancer^{1,2}. This raised concerns among some clinicians and people with diabetes. Following these publication, FDA and the EMA independently undertook comprehensive evaluations using multiple streams of data of the safety signal arising from reports of pancreatitis and pancreatic cancer in people using incretin-based medications³. Both agencies stated that the reported causal association between incretin-based therapy and pancreatitis or pancreatic cancer, are inconsistent with the existing data. They also explained that although the totality of the data that had been reviewed provided reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available, and that both agencies continue to investigate this safety signal.

This position statement aims to weigh up current evidence in order to make recommendations for clinicians as well as people with diabetes currently taking incretin therapy, or considering these as a treatment option.

How did we develop this position?

This position statement was put together through a comprehensive review of literature, and discussions with healthcare professionals.

What we say about this issue

- There is no proven causal link between the use of incretin therapy and pancreatic cancer
- Diabetes UK does not advocate any change in management of incretin therapy and await more research on the subject.

- People with diabetes should NOT stop their medication, without discussing this with their healthcare team.
- Vigilance is required of people on such therapies for any side effects suggestive of pancreatic disease. These symptoms may include upper abdomen pain, jaundice, weight loss, nausea, loss of appetite and fever.
- Clinicians and people with diabetes should be aware that incretin therapies are contraindicated in people with previous pancreatitis.

It is important that any medication, particularly relatively modern therapies such as incretin therapy, should be used in line with current guidance for appropriate patients. Subsequent monitoring of outcomes should also be acted upon in keeping with guidance, including stopping treatment where the therapy is not shown to have the agreed benefits.

Evidence and analysis

A study has suggested a potential risk of asymptomatic chronic pancreatitis and, with time, pancreatic cancer¹ with incretin therapy, compared to older agents. However, reporting bias cannot be excluded, as adverse events are more likely to be reported with newer agents. In addition, the methodology of the research has given rise to some discussion among specialists and there is consensus that the research findings, though interesting, have limitations. More recently, a large international multicentre study⁴ and a meta-analysis of randomised controlled studies⁵ have both concluded that the use of incretin-based therapies are not associated with increased risk of pancreatic cancer.

Pancreatic cancer and pancreatitis are commoner in obese people⁶ and in people with Type 2 diabetes³. Acute and chronic pancreatitis, more common in people with Type 2 diabetes, are also risk factors for pancreatic cancer^{8,9}. Thus study which found an increased risk of pancreatitis and pancreatic cancer with the two GLP-1 drugs available at the time¹ must be interpreted with caution because of the complex relationships involved with obesity, diabetes, and treatments of diabetes. To put these risks into perspective, smoking is the commonest cause of pancreatic cancer and explains about 25% of the entire burden of disease with smokers having about a two-fold increased risk compared with non-smokers¹⁰.

All drugs undergo careful testing under research trial conditions before they are licensed for use. However, these trials generally involve relatively small numbers of

participants for short periods of time. Common side effects generally come to light during such testing, but rare side effects are usually not identified until the drug is used in routine clinical practice, in large numbers of people for long periods.

In diabetes, trials of drugs usually look at effects on “intermediate endpoints” which change quickly, such as glucose control or weight. Information about their effects on hard outcomes such as heart disease or retinopathy takes much longer to gather and so is usually not available for some years after the drug is licensed.

Thus the decision to use any new drug in diabetes must involve weighing up the known and potential benefits against the known and unknown side-effects.

References

1. Elashoff M¹, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology*. 2011 Jul;141(1):150-6.
2. Butler AE¹, Campbell-Thompson M, Gurlo T, Dawson DW, Atkinson M, Butler PC. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes*. 2013 Jul;62(7):2595-604. doi: 10.2337/db12-1686. Epub 2013 Mar 22.
3. Egan AG, Blind E, Dunder K, de Graeff PA, Hummer BT, Bourcier T, Rosebraugh C. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med*. 2014 Feb 27;370(9):794-7.
4. Azoulay L, Filion KB, Platt RW, Dahl M, Dormuth CR, Clemens KK, Durand M, Juurlink DN, Targownik LE, Turin TC, Paterson JM, Ernst P; Canadian Network for Observational Drug Effect Studies Investigators. Incretin based drugs and the risk of pancreatic cancer: international multicentre cohort study. *BMJ*. 2016 Feb 17;352:i581.
5. Chen H, Zhou X, Chen T, Liu B, Jin W, Gu H, Hong T, Zhang G. Incretin-Based Therapy and Risk of Pancreatic Cancer in Patients with Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Controlled Trials. *Diabetes Ther*. 2016 Dec;7(4):725-742.
6. Wang SQ, Li SJ, Feng QX, Feng XY, Xu L, Zhao Q. Overweight is an additional prognostic factor in acute pancreatitis: a meta-analysis. *Pancreatology*. 2011;11(2):92-8. Epub 2011 May 17.
7. Lai SW, Muo CH, Liao KF, Sung FC, Chen PC. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. *Am J Gastroenterol*. 2011 ep;106(9):1697-704.

8. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andrén-Sandberg A, Domellöf L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med*. 1993 May 20;328(20):1433-7.
9. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterology*. 1995 Jul;109(1):247-51.
10. Fuchs CS, Colditz GA, Stampfer MJ, Giovannucci EL, Hunter DJ, Rimm EB, Willett WC, Speizer FE. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med*. 1996 Oct 28;156(19):2255-60.