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Incretin-based therapy: Is the risk of pancreatitis driven by cardiovascular disease?

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ABSTRACT

Incretin-based therapies are normally prescribed to individuals with type 2 diabetes but has recently come under scrutiny due to the possibility of associated pancreatitis. A 2014 systematic review published in the *BMJ* found no increase risk of acute pancreatitis in adults with type 2 diabetes, as partly evident from the meta-analysis of RCTs (OR = 1.11, 95% CI 0.57–2.17). By contrast, a second meta-analysis added 3 large outcome trials in patients with previous cardiovascular disease to the previous 55 RCTs from Li et al. and showed an increased risk in acute pancreatitis. While the discrepancy in result may be due to better quality large trials, as the authors suggest, it is likely that since the large outcome trials investigated patients with cardiovascular disease, the increased risk is present only in this group.

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Incretin-based therapies are prescribed to individuals with type 2 diabetes owing to good glucose-lowering effects, weight neutrality, and a reduced risk of hypoglycemia [1,2]. But use of incretin-based therapies has come under scrutiny due to a possible association with pancreatitis. A 2014 systematic review published in the *BMJ* investigated this putative effect with 55 randomized control trials (RCTs), typically phase III, and 5 observational studies [3]. The authors concluded that incretin-therapies do not increase risk of acute pancreatitis in adults with type 2 diabetes, as partly evident from the meta-analysis of RCTs (OR = 1.11, 95% CI 0.57–2.17).

Following publication of these results, a subsequent meta-analysis of RCTs by Roshanov and Dennis [4] added 3 large outcome trials to the previous 55 RCTs from Li et al. Addition of these 3 trials showed an increased risk of acute pancreatitis

from incretin-therapies (OR = 1.54, 95% CI 1.07–2.21) [4]. With the 3 trials alone, the results demonstrated an even higher risk (OR = 1.76, 95% CI 1.14–2.72). A presentation by R. Holman at World Diabetes Congress 2015 was consistent with these results [5]. To explain the apparent differences in results, Roshanov and Dennis stated that larger trials likely overcome biases that plague meta-analyses of smaller studies. However, there may be other more plausible explanations.

Notably, there are differences in the populations studied and duration of follow-up between the 3 large outcome trials and RCTs included in Li et al. The 3 large-outcome trials focus on patients with cardiovascular co-morbidities. Specifically, patients in the SAVOR-TIMI 53 trial [6] had either a history of established cardiovascular disease (CVD) or multiple risk factors for vascular disease. Similarly, the EXAMINE trial [7]

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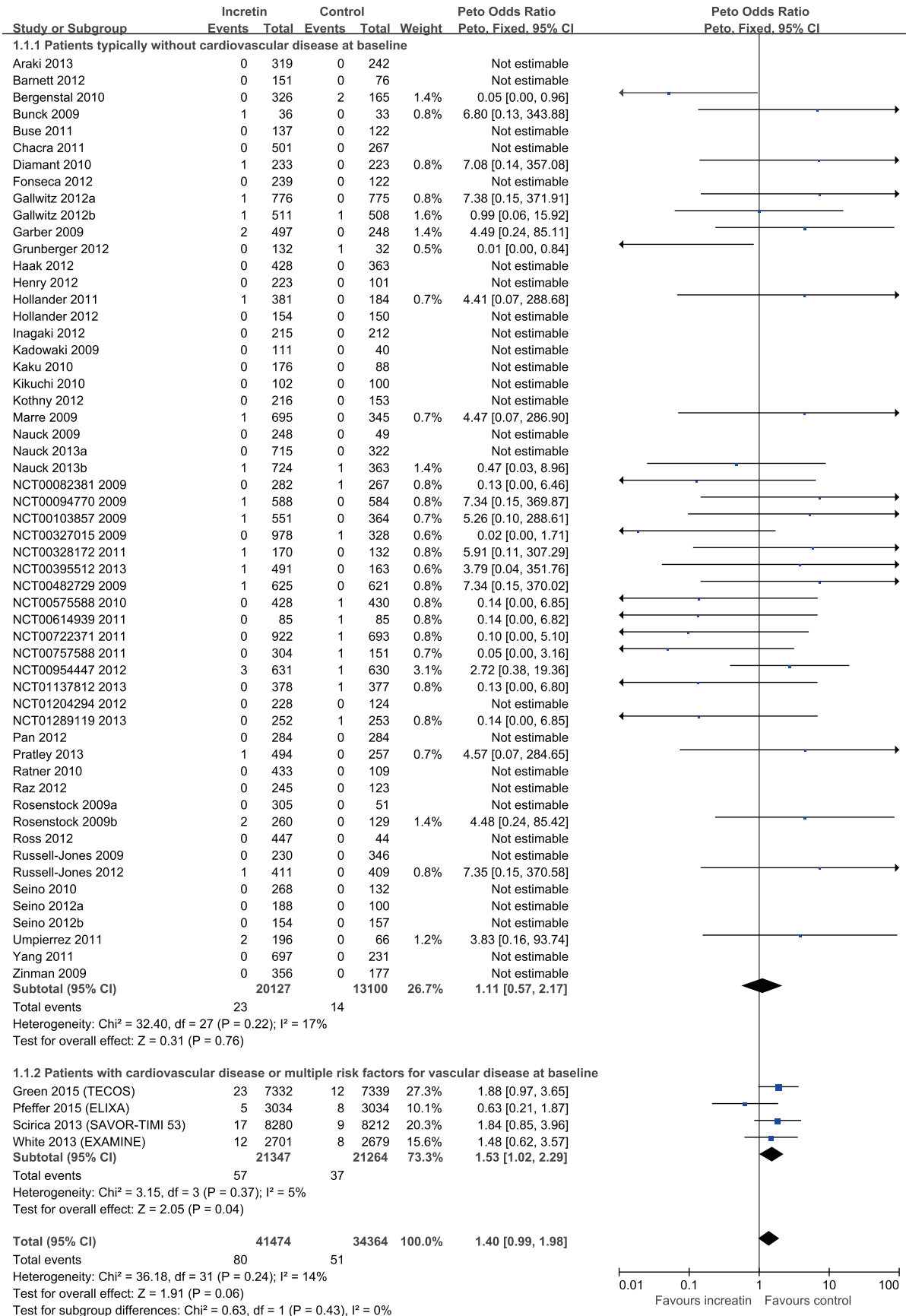


Fig. 1 – Forest plot of all 59 studies investigating effect of incretin-therapy on acute pancreatitis, with subgroups.

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