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Icosapent Ethyl in Addition to Statins Is a Cost-Effective Treatment in Patients at High Cardiovascular Risk with Elevated Triglycerides and Established Cardiovascular Disease or Diabetes with Risk Factor in The Netherlands

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INTRODUCTION

- Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in Europe. CVD encompasses a broad group of medical conditions that affect the circulatory system, such as myocardial infarction (MI), peripheral arterial disease, and stroke.[1] These often lead to chronic complaints, disability, secondary diseases, loss of quality of life, increased health care system utilization, and death.
- The economic burden of CVD is high: CVD costs the EU economy an estimated €210 billion per year, of which 53% is attributable to direct health care costs, 26% to productivity losses and 21% to informal care.[2] The COVID-19 pandemic's disruption of access to acute care and preventive measures have only increased the societal burden of CVD.[3] This highlights the need for preventative measures that lead to a proven reduction in cardiovascular (CV) events and CV mortality.
- Patients with established CVD (eCVD) and patients with diabetes have an increased risk of CVD. Statin therapy significantly reduces CV morbidity and mortality. However, up to 40% of statin-treated patients continue to experience life-threatening CV events, even if the LDL cholesterol goal is achieved through intensive statin treatment.[4]
- Icosapent ethyl, a new active substance, is a highly purified ethyl ester of eicosapentaenoic acid and is proven and indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high CV risk with elevated triglycerides (TG) (≥150 mg/dL) and 1) eCVD or 2) diabetes and at least one other CV risk factor.[5]
- The Dutch Healthcare Institute recently concluded that the effect of icosapent ethyl was considered clinically relevant for the entire indicated population but recommended for reimbursement only in the eCVD population: the population with the highest CV risk where treatment with icosapent ethyl as secondary prevention yields most benefit.[6]

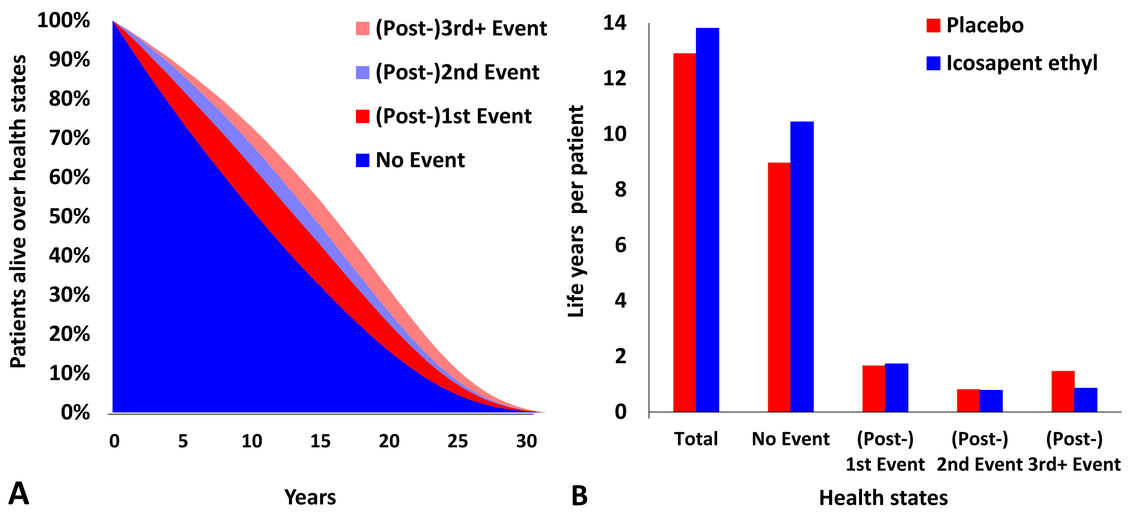
OBJECTIVE

- This study estimated the cost-effectiveness of icosapent ethyl versus placebo on top of statins in adult patients at high CV risk with elevated TG (≥150 mg/dL) and 1) eCVD, or 2) diabetes and at least one other CV risk factor, from a societal perspective in The Netherlands in 2021.

METHODS

- A cost-utility model was developed as a partitioned-state survival model with a cycle length of 1 day. The model analyzed costs and effects over a lifetime (36-year) horizon.
- Health states were defined by the occurrence of a (post-)first, (post-)second, or (post-)third or subsequent CV event, defined as MI, stroke, unstable angina (UA), coronary revascularization (CR), or CV death. Death, either CV-related or non-CV-related, was the absorbing state.
- Each event health state was divided into acute and post-acute phases:
  - CV event states represent acute phases with a duration of 1 day.
  - Post-CV event states succeed acute events. Patients remain in a post-CV event state until they experience a subsequent CV event.
- Population characteristics and clinical model inputs were derived from the REDUCE-IT clinical trial of icosapent ethyl versus placebo on top of statins. The intention-to-treat (ITT) cohort of REDUCE-IT consisted of males and females 1) aged ≥45 years with eCVD or 2) aged ≥50 years with diabetes in combination with ≥1 risk factor for CVD. They had LDL-C levels >40 - ≤100 (mg/dL) and TG levels ≥135 - <500 (mg/dL) on stable statin therapy for at least four weeks and were followed for a median duration of 4.9 years.[7]

Figure 1. Icosapent ethyl patients alive distributed over each health state (A) and patients' life years in each health state (B)



- Health state occupancy (Figure 1) was estimated using a partitioned-state survival model of time-to-CV events. To this end, parametric models were fit to the time-to-event data from REDUCE-IT with treatment as covariate and extrapolated beyond the trial duration. The time-to-first CV event and time-to-treatment discontinuation followed an exponential distribution, and time-to-second and third or more CV events were modelled according to the log-logistic distribution following NICE guidelines.[8] The probability of CV-related mortality was dependent on patients' health state and cohort, i.e. eCVD or high-risk diabetes.
- Health-related utility values and costs were linked to each (post-)event health state. Drug acquisition, disease management, adverse event (AE) costs, and AE disutilities were included as well as travel costs, caregiver costs, and productivity losses as per the Dutch HTA requirements for health economic evaluation.[9] All costs were indexed to the reference year 2021.
- Drug costs for icosapent ethyl were set at a list price of €200 per pack of 120 capsules, a daily price of €6.68. Daily drug costs for statin treatment ranged between €0.02 - €0.12. Table 1 shows health state costs for acute and post CV events.

Table 1. CV event health state costs

CV event	Acute health state (one-off cost)	Post-event health state (daily)
Nonfatal MI	€5,454.98[13]	€8.30
Nonfatal stroke	€20,243.76[13]	€12.03
Coronary revascularization	€6,806.02[14-15]	€5.48
Unstable angina	€3,441.64[16]	€3.92
CV death	€ 7,529.28[13]	-

- Utility values in the event-free state were 0.77[10] for the eCVD and 0.75[11] for the high-risk diabetes cohorts. When a first, second or third event occurred, the patient's current health state utility value was multiplied with event-specific utility multipliers[12] to obtain the new (post-)event health state utility value.
- Outcomes were calculated over a lifetime horizon for the ITT population and the subgroup of eCVD patients. Costs were discounted at 4%, effects at 1.5%.[9]
- Univariate and probabilistic sensitivity analyses, and scenario analyses were conducted to quantify the impact of uncertainty around input parameters and assumptions.

RESULTS

- The incremental discounted results of icosapent ethyl versus placebo on top of statins in the ITT population were 0.438 life years, 0.521 quality-of-life years (QALYs), and €9,595 costs (Table 2).
- The resulting incremental cost-effectiveness ratio (ICER) of €18,415/QALY was in line with the relevant Dutch reference willingness-to-pay threshold (WTP) of €20,000/QALY, based on the iMTA calculated burden of disease for the ITT population.[11]
- The incremental discounted results for the eCVD sub-population were 0.542 life years, 0.633 QALYs and €9,216 costs, yielding an ICER of €14,553/QALY (Table 2).

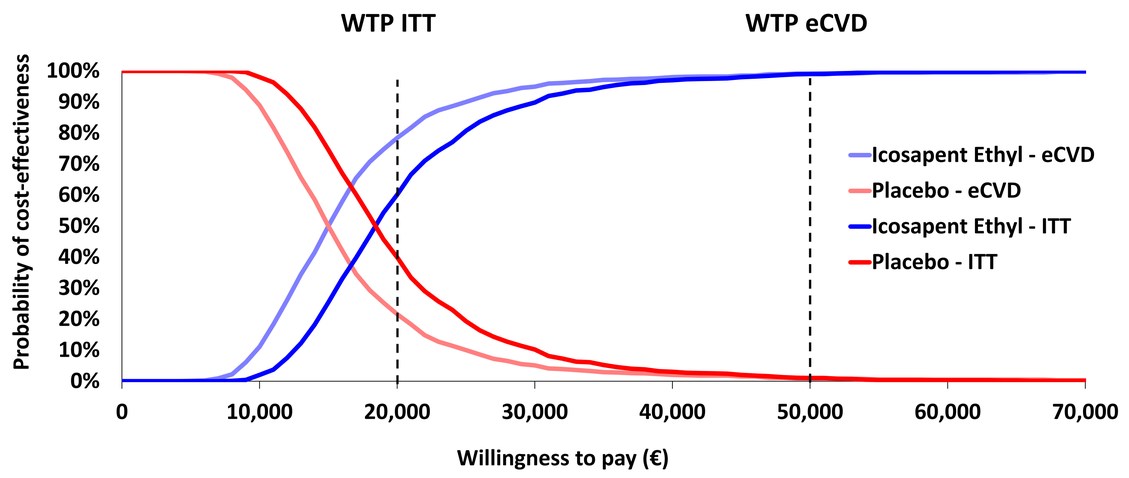
Table 2. (Incremental) discounted results for the ITT and eCVD populations

	ITT			eCVD		
Outcomes	Icosapent ethyl	Placebo	Difference	Icosapent ethyl	Placebo	Difference
Costs (€)	30,101	20,507	9,595	32,404	23,187	9,216
Life years	13.341	12.902	0.438	13.140	12.598	0.542
QALYs	9.603	9.082	0.521	9.453	8.820	0.633
ICER	Icosapent ethyl vs placebo: €18,415/QALY			Icosapent ethyl vs placebo: €14,553/QALY		

NB: Values in table are rounded

- Main drivers of the incremental costs were the costs associated with experiencing a third (or more) CV event and costs associated with acute CR. Baseline utility in the eCVD subgroup and health state utilities were the main drivers of incremental QALYs as well as the ICER in both populations.
- At a WTP threshold of €20,000/QALY, icosapent ethyl had a 60.1% probability to be cost-effective in the ITT population. Icosapent ethyl had a 99.1% probability to be cost-effective in the eCVD population, at the for this sub-population relevant reference WTP of €50,000/QALY (Figure 2).
- Scenarios shortening the time horizon to 10 years, increasing the discount rates to 6%, or including indirect medical costs had most impact on the model outcomes for both populations, elevating the ICER to €60,000, €32,000 and €25,000/QALY for the ITT population, respectively.
- Modest changes in the cost-effectiveness outcomes were found for scenarios changing parametric survival distributions, changing to healthcare perspective, and excluding productivity losses, travel costs, and caregiver costs.

Figure 2. Cost-effectiveness acceptability curve for the ITT and eCVD cohorts



CONCLUSIONS

- At a WTP reference value for the ITT population of €20,000/QALY, treatment with icosapent ethyl is cost-effective compared to current Dutch standard practice of statin treatment only, with a predicted ICER value of €18,415 and a 60.1% probability of being cost-effective.
- Treatment with icosapent ethyl is cost-effective compared to current standard practice as well for the subgroup of patients with eCVD, at a reference value of €50,000/QALY, with a predicted ICER value of €14,553 and a 99.1% probability of being cost-effective.
- The conducted sensitivity and scenario analyses showed the cost-effectiveness model outcomes were robust to uncertainty around model inputs and the main model assumptions.

REFERENCES

1. Mach F, et al. *Eur Heart J* 2020;41(1):111-88.
2. Wilkins E, et al. European Cardiovascular Disease Statistics 2017; Brussels: European Heart Network.
3. Pina A, et al. *Curr Cardiol Rep* 2021;23(10): 135.
4. Cho KI, et al. *Circ J* 2019;83(10):1973-1979.
5. European Medicines Agency. SmPC Vazkepa® (icosapent ethyl) 2021.
6. Zorginstituut Nederland. GVS-advies icosapent ethyl (Vazkepa®), 16 September 2022.
7. Bhatt DL, et al. *N Engl J Med 2019;380(1):11-22*.
8. Latimer N, et al. 2013 NICE DSU Technical Support Document 14.
9. Hakkaart-van Roijen L, et al. 2015 Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg.
10. Stevanovic J, et al. *PLoS One* 2016;11(3):e0152030.
11. O'Reilly DJ, et al. *Qual Life Res* 2011;20(6):939-43.
12. National Institute for Health and Care Excellence. 2021 Clinical guideline cardiovascular disease CG181.
13. Burgers LT, et al. *Int J Cardiol* 2014;176(3):980-7.
14. Nederlandse zorgautoriteit. 2021 OpenDISData: DBC-zorgproduct 979001225.
15. Nederlandse zorgautoriteit. 2021 OpenDIS data: DBC-zorgproduct 979001071.
16. Nederlandse zorgautoriteit. 2021 OpenDIS data: DBC-zorgproduct 099499017.
17. iDBC. iMTA Disease Burden Calculator; Accessed 24 August 2021.

DISCLOSURES

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