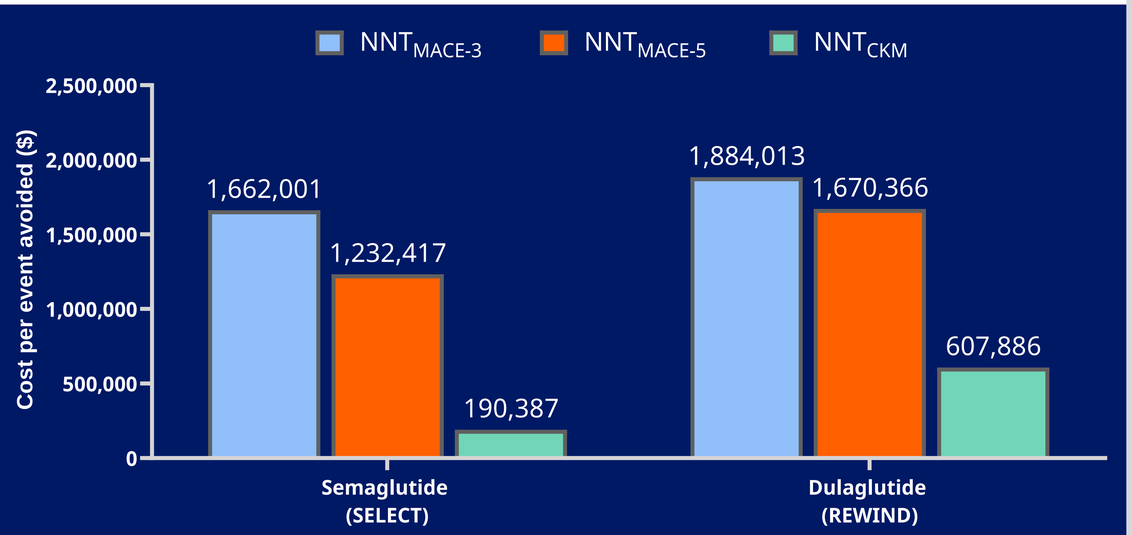
Utilizing a composite number needed to treat to assess the clinical and economic value of semaglutide and dulaglutide in populations with established cardiovascular disease

Poster code: EE155

Joshua Toliver[1]; Julia Wang[1]; Jigish Bhavsar[1]; Sean D. Sullivan[2, 3]

Utilizing a **composite number needed to treat (NNT)** and **cost per event avoided** that includes outcomes beyond only the primary endpoint of a treatment captures the comprehensive value of a treatment.



Aim

- To evaluate multiple hierarchical numbers needed to treat (NNTs), and associated cost per event avoided.
- To demonstrate a more comprehensive value of treatment by comparing different methods of calculating NNT and cost per event avoided using multiple composite endpoints.

Background

- Cardiovascular disease (CVD) is a leading cause of mortality worldwide and contributes substantially to morbidity, namely through major adverse cardiovascular events (MACE)[1]. **Table 1** summarizes how MACE were defined in this study.
- CVD has been linked to risk factors such as obesity, type 2 diabetes (T2D) and chronic kidney disease (CKD), referred to as cardiovascular-kidney-metabolic (CKM) syndrome[2].
- Treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has a well-established role in regulating blood glucose levels and weight management[3]. There is growing evidence for GLP-1 RAs to provide benefits in treating CVD and CKD[4,5].
- The SELECT (NCT03574597) trial has shown that once-weekly subcutaneous semaglutide (2.4 mg GLP-1 RA) treatment is superior to placebo in reducing MACE in people living with CVD and overweight or obesity, but without T2D[6].
- The REWIND (NCT01394952) trial has shown that once-weekly subcutaneous dulaglutide (1.5 mg GLP-1 RA) treatment reduces the risk of MACE in people living with CVD and controlled T2D[7].
- NNT is a measure of absolute effect used to represent the clinical value of therapeutic treatments and is commonly used to assess the benefit of a treatment[8,9].
- NNT is derived from the risk result of randomized controlled trials to describe the number of patients treated with one therapy versus another to prevent one event or to encounter one additional outcome of interest within a predefined time-period[9,10].
- Though effective, NNT has its limitations in that it is often calculated using the primary endpoint[11].
- Estimating NNTs by utilizing multiple composite endpoints could better capture the treatment benefit, as has been demonstrated by a recent analysis from the SELECT trial[11].
- NNTs are often utilized to derive the cost per event avoided to understand the economic value of a treatment. Despite this evaluation being utilized as a simple measure, full cost effectiveness analyses should be used as the standard for evaluating economic value[12].
- **This study offers a novel approach to considering a more comprehensive value of a therapy** by estimating NNT and the cost per event avoided using multiple composite endpoints. Data from the SELECT and REWIND trials were used to assess this approach.

Methods

- This was a post-hoc analysis of two cardiovascular outcome trials, SELECT (semaglutide 2.4 mg)[6] and REWIND (dulaglutide 1.5 mg)[7].
- A summary of the endpoints included in the calculation of each cost per event avoided for each study is defined in **Table 1**.

Table 1: Endpoints included for each cost per event avoided calculation

	MACE-3	MACE-5	SELECT CKM (Semaglutide)	REWIND CKM (Dulaglutide)
Myocardial infaction	✓	✓	✓	✓
Stroke	✓	✓	✓	✓
Cardiovascular death	✓	✓	✓	✓
All-cause mortality			✓	✓
Hospitalization due to unstable angina		✓	✓	✓
Hospitalization due to heart failure		✓	✓	✓
Coronary revascularization			✓	
Type 2 diabetes ($HbA_{1C} \geq 6.5\%$)			✓	
5-point nephrology			✓	
Microvascular outcomes				✓

CKM: Cardiovascular-kidney-metabolic syndrome; MACE-3: cost per 3-point major adverse cardiovascular event; MACE-5: cost per 5-point major cardiovascular event.

- NNT outcomes were calculated for each composite endpoint (cost per 3-point MACE [MACE-3], cost per 5-point MACE [MACE-5], and cost per CKM event [CKM]) by using the following equation:

$$NNT = \frac{1}{Absolute\ risk\ reduction\ (ARR)} \text{ where}$$
$$ARR = control\ event\ rate - experimental\ event\ rate$$

- Cost per event avoided was calculated for each composite endpoint as:

$$Cost\ per\ event\ avoided = NNT \times duration\ of\ treatment/follow\ up^{*} \times estimated\ net\ price^{\ddagger}$$

*For duration of follow-up, the mean (± standard deviation [SD]) value was used for semaglutide and the median (interquartile range [IQR]) value was used for dulaglutide.
‡Estimated monthly net prices for semaglutide and dulaglutide can be found in **Table 2.**

Results: Cost per event avoided and NNT

- For both semaglutide and dulaglutide treatment, a **lower NNT was observed as more outcomes were included**, where $NNT_{MACE\text{-}3}$, $NNT_{MACE\text{-}5}$, and NNT_{CKM} were 67, 49, and 8 for semaglutide, and 72, 64, and 23 for dulaglutide, respectively (**Table 2**).
- A **lower cost was observed as the number of outcomes increased** in each composite endpoint, where cost per event $avoided_{MACE\text{-}3}$, cost per event $avoided_{MACE\text{-}5}$, and cost per event $avoided_{CKM}$ were $1,662,001, $1,232,417, and $190,387 for semaglutide treatment and $1,884,013, $1,670,366, and $607,886 for dulaglutide treatment, respectively **(Table 2).**

Table 2: NNT and cost per event avoided **Key result**

	Semaglutide (SELECT)	Dulaglutide (REWIND)
$NNT_{MACE\text{-}3}$	67	72
$NNT_{MACE\text{-}5}$	49	64
NNT_{CKM}	8	23
Cost per event $avoided_{MACE\text{-}3}$	$1,662,001	$1,884,013
Cost per event $avoided_{MACE\text{-}5}$	$1,232,417	$1,670,366
Cost per event $avoided_{CKM}$	$190,387	$607,886
Duration of treatment/follow-up (months)	34.2 ± 13.7 (Mean ± SD)	64.8 [61.2; 70.8] (Median [IQR])
Estimated monthly net price*	$717	$403

*Estimated monthly net price based on Hernandez and Sullivan, 2024[13]. CKM: Cardiovascular-kidney-metabolic syndrome; MACE-3: cost per 3-point major adverse cardiovascular event; MACE-5: cost per 5-point major cardiovascular event.

Summary

- A secondary post-hoc analysis was conducted on the SELECT and REWIND clinical trials which took into account the estimated NNT and cost per event avoided by utilizing multiple composite endpoints to capture the comprehensive value of a therapy.
- For semaglutide and dulaglutide treatment, a lower NNT was observed as more outcomes were included.
- A lower cost per event avoided was observed as the number of outcomes increased.

Limitations

- Economic value should be evaluated through cost-effectiveness models. Cost per event avoided and NNTs are often used as a simple measure.
- The focus of this study was to understand the impact of different outcomes on NNT/cost per event avoided within each treatment, and not to compare these values between treatments.
- Cross-trial comparisons between treatments should be made with caution due to differences between trials.

Conclusion

- This study demonstrates the limitations of using a methodology that focuses only on primary endpoints to generate NNT/cost per event avoided, because it does not capture the comprehensive benefit of the treatment.
- When utilizing NNT and cost per event avoided to evaluate value of a treatment, outcomes beyond the primary endpoint should be taken into account to understand the comprehensive value. Further research is needed to demonstrate how this methodology can be used to compare treatments across trials.

[1]Novo Nordisk Inc., Plainsboro, NJ, USA; [2]Curta Inc., Seattle, WA, USA; [3]CHOICE Institute, School of Pharmacy, University of Washington, Seattle, WA, USA
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