

Cost-effectiveness of landiolol, an ultra-short-acting beta-blocker, for treatment of Sepsis related Tachyarrhythmia in Germany

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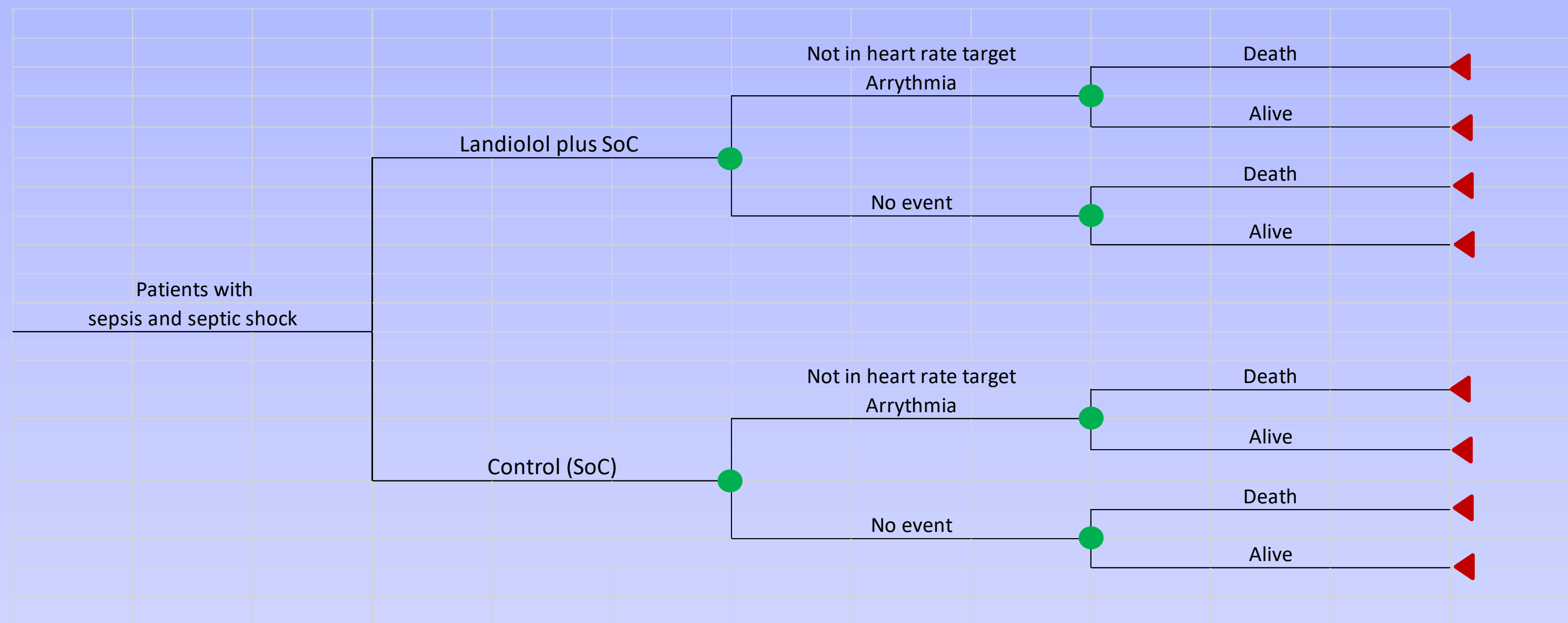
Objectives

Sepsis and septic-shock are associated with cardiovascular problems, including tachyarrhythmia, myocardial injury, and changes in vascular endothelial function that might affect cardiac output with potential fatal outcome. The consequences of sepsis extend well beyond the acute illness. Tachycardia and new-onset atrial-fibrillation, often treated with less effective agents such as amiodarone, are key prognostic factors for sepsis and associated with increased use of health-care resources and costs. Early decrease of heart-rate is associated with improved outcome. The use of β -blockers for managing acute arrhythmias in patients with septic-shock has been described in the literature. Landiolol, an ultra-short-acting β 1-selective adrenergic-receptor-antagonist, is used specifically for the acute management of atrial-fibrillation and atrial-flutter in critically-ill patients with/without cardiac-dysfunction. The aim of this analysis is to analyze the cost-effectiveness of landiolol (Rapibloc®) versus standard of care (SoC) to reduce mortality, avoid new-onset arrhythmia and to aim that patients reach a heart rate of 60–94 bpm within 24 hour (h). The health economic analysis should assess health economic advantages of using landiolol in the acute care in patients with sepsis or septic shock from the hospital perspective. No analyses have yet been carried out to determine the cost-effectiveness of landiolol for treatment of sepsis-related tachyarrhythmia.

Methods

A decision-model was developed to reflect the cost-effectiveness of landiolol in addition to conventional-therapy vs. SoC to manage sepsis-related tachyarrhythmia. The model benefit was expressed in a percentage change of patients with new-onset arrhythmia and mortality. Clinical data were derived from a clinical-trial of Kakihana et al. (2020) involving 151 patients. The model calculates total inpatient costs (incl. hospital-stay, ICU and ventilation) over the hospital-length-of-stay (LOS). Costs (€) based on data for the year 2020 from published sources were used from the German hospital perspective. A one-way deterministic-sensitivity-analysis accounts for uncertainty.

Fig. 1: Model Design



Source: own developed

Clinical Data

The economic model of landiolol was designed based on a single clinical trial of Kakihana et al. (2020), a multicentre, open-label, randomised controlled trial at 54 hospitals in Japan. Patients admitted to the intensive care units who received conventional treatment for sepsis, according to clinical guidelines for the management of sepsis, and who subsequently developed a tachyarrhythmia, were enrolled..

- The primary outcome was the proportion of patients with heart rate of 60–94 bpm 24 h after randomisation. Patients without heart rate data 24 h after randomization were handled as non-responders
- Secondary efficacy outcomes included changes in heart rate, proportion of patients with a decrease in heart rate of 20% or more (baseline and 24 h, 48 h, 72 h, and 96 h after randomisation), proportion of patients whose heart rate was controlled to 60–94 bpm (up to 96 h), proportion of participants with new-onset arrhythmia (by 168 h), ICU free days (by 28 days), hospital-free days (by 28 days), 28-day mortality, and clinically relevant parameters (Kakihana et al. 2020).

Tab. 1: Primary and secondary endpoints

Primary and secondary endpoints	Landiolol (N=75)	Control (N=75)	Between group difference (95% CI)	Hazard ratio (95% CI)	P value
Patients with heart rate of 60-94 bpm at 24h	41 (55%)	25 (33%)	23.1% (7.1-37.5)	-	0.0031
Patients with new-onset arrhythmia by 168 h	7 (9%)	19 (25%)	-	0.36 (0.15-0.85)	0.015
Ventilator-free days	17.0 (11.1)	17.9 (11.5)	-	-	0.47
Intensive care unit-free days	14.6 (8.6)	13.3 (9.1)	-	-	0.55
Hospital-free days	1.6 (3.8)	1.8 (4.2)	-	-	0.91
Death by day 28	9 (12%)	15 (20%)	-	0.60 (0.26-1.37)	0.22

Source: Kakihana et al. 2020

Resource Use and Costs

Resource use data were derived based on literature search including German data to reflect the German clinical practice. The CEA collects total costs including hospital stay costs (normal ward), ICU costs and costs for ventilation. Medication costs of vasopressors are covered in the German G-DRG lump sum. All costs were derived from public price lists, tariff catalogues and the literature. Due to the short time horizon of the model, discounting of costs is not necessary.

Results

Patients with sepsis-related tachyarrhythmia had a higher incidence of mortality, morbidity and LOS including ICU, a more frequent ventilation requirement and finally higher costs; new-onset arrhythmia occurred in 9.3% of cases and 12% of patients died within 28 days. Despite additional per patient costs of landiolol, landiolol is able to reduce hospital costs of 38,550€ (95%-CI=34,216–43,374; p-value=0.004) against SoC by-1,375.65€ and decreases new-onset arrhythmia by 64% [HR:0.357 (95%-CI=0.150–0.849; p-value=0.015]. Mortality declined by 40% when using landiolol [HR:0.599 (95%-CI=0.262–1.370; p-value=0.22]. Landiolol dominates SoC.

Tab. 2: Cost-effectiveness results

Cost Components	Landiolol	Control	Difference
Costs hospital stay (nomal ward)	16,195.69	16,072.99	122.69
Costs ICU stay	22,353.87	23,852.22	-1,498.34
Total costs	38,549.56	39,925.21	-1,375.65
Survival	88.0%	80.0%	8.0%
Additional costs/savings per fatal case avoided (ICER)			-17,195.60*
No new-onset of arrhythmia	90.7%	74.7%	16.0%
Additional costs/savings per patients with arrhythmia avoided (ICER)			-8,597.80*
Patients reaching heart rate target	54.7%	33.3%	21.3%
Additional costs/savings per patient reaching HR target (ICER)			-6,448.35*

ICER = incremental cost effectiveness ratio
Source: own calculations

*Landiolol dominates Control

Due to a lower need for ICU days (13.4 vs. 14.7 days), hospital costs in the landiolol group can be significantly reduced, despite the higher need for ventilation in the landiolol group (11 vs 10.1 days) (see Fig. 2A). The ICER shows a negative result for all endpoints, i.e. landiolol is able to generate savings in the German hospital setting (Fig. 2B).

Fig. 2A: Average cost in the landiolol-group or controls

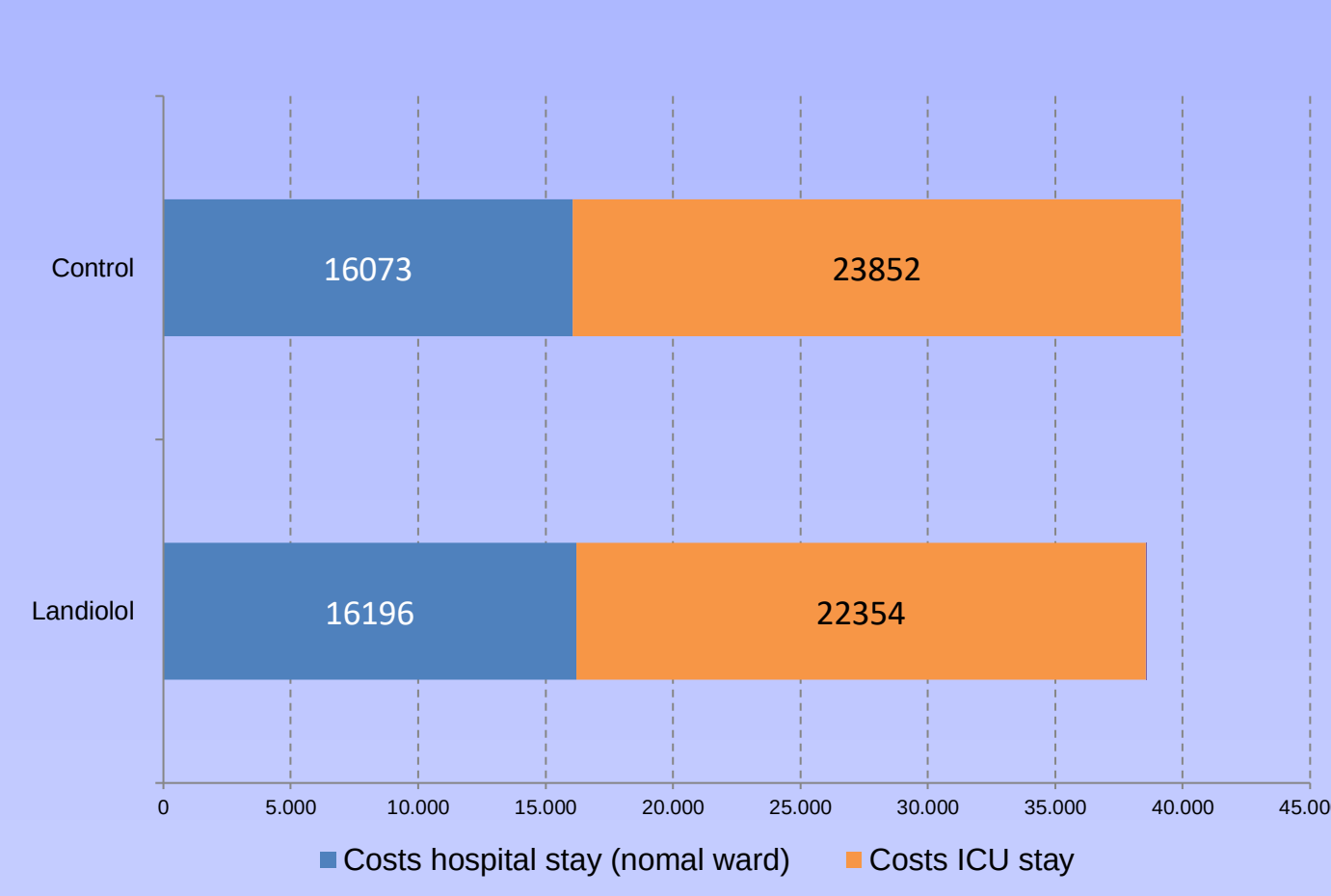
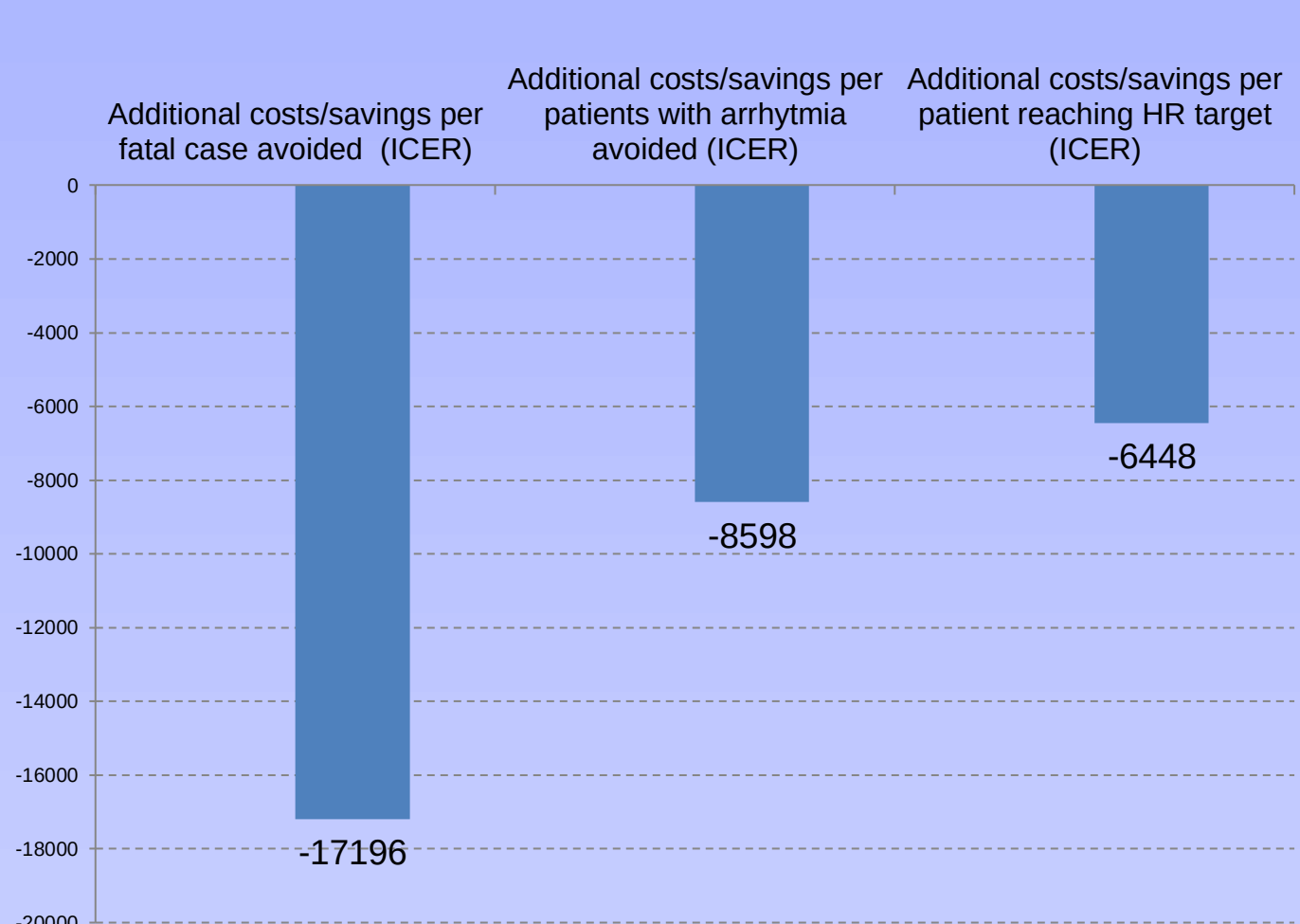


Fig. 2B: ICER for different endpoints

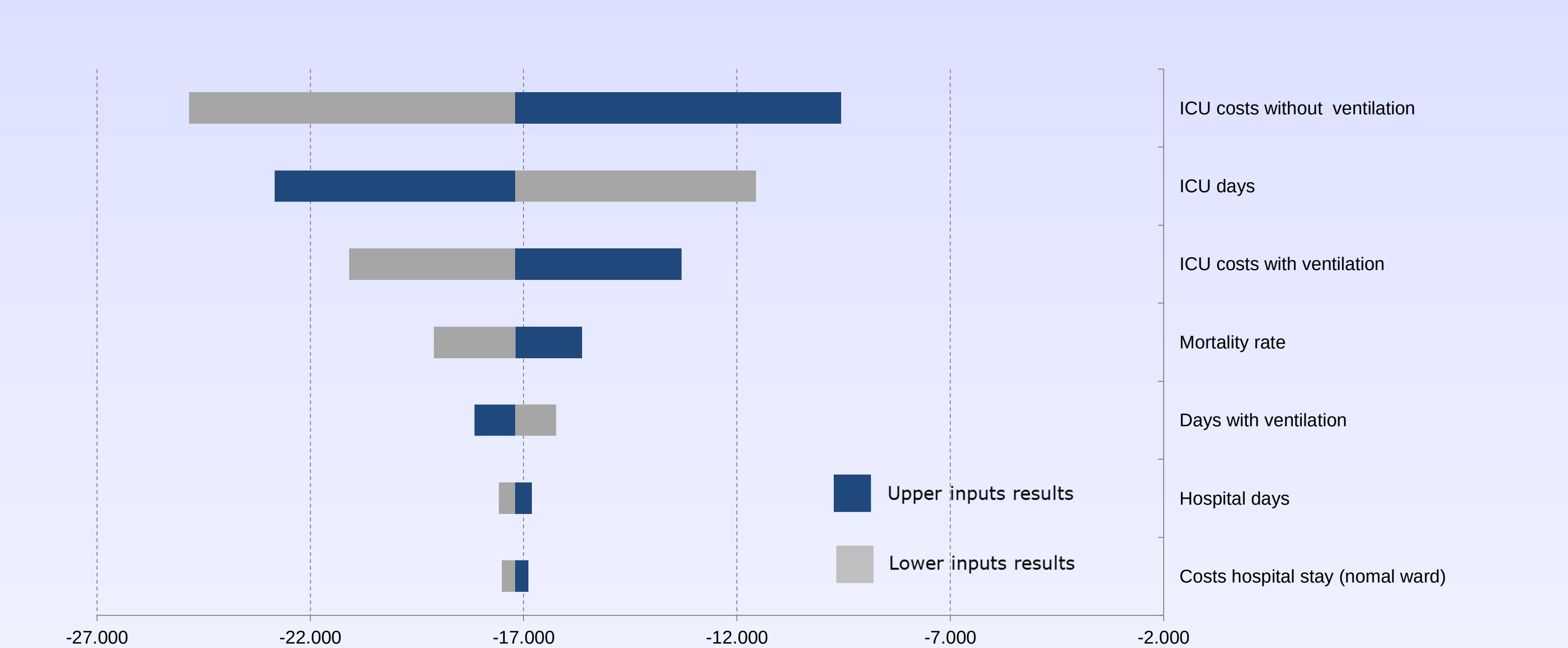


ICER = incremental cost effectiveness ratio
Source: own calculations

Sensitivity Analysis

Deterministic one-way sensitivity analysis (OWSA) was carried out. Fig. 3 displays results for the population. The results of the OWSA show the range of the ICER (incremental cost effectiveness ratio; outcome mortality) due to variation of a single input parameter. ICERs of landiolol versus control ranged from -16,237.23 to -18,153,.97 €. The effect on costs of ICU stay and ICU days show the greatest influence. Landiolol remains the dominant strategy in all variations of OWSA.

Fig. 3: Probabilistic OWSA



Source: own calculations

Conclusion

The economic analysis of landiolol shows that the use is highly cost-effective, represents the lowest total cost, and is associated with a superior effect. Landiolol generates cost savings from the hospital perspective as well as the German payer's perspective.

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