Cost-Effectiveness of Alirocumab Based on Evidence From a Large Multinational Outcome Trial: The ODYSSEY OUTCOMES Economics Study

Deepak L. Bhatt, Andrew Briggs, Shelby D. Reed, Lieven Annemans, Michael Szarek, Vera A. Bittner, Rafael Diaz, Jay M. Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert A. Harrington, J. Wouter Jukema, Kenneth W. Mahaffey, Angèle Moryusef, Robert Pordy, Matthew T. Roe, Robert J. Sanchez, Keiko Higuchi, Renato D. Lopes, Harvey D. White, Andreas M. Zeiher, Gregory G. Schwartz, Ph. Gabriel Steg
On behalf of the ODYSSEY OUTCOMES Investigators and Committees

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ClinicalTrials.gov: NCT01663402

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, Amarin, **Amgen**, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, **Regeneron**, Roche, **Sanofi Aventis**, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, PLx Pharma, Takeda.

- **This presentation includes off-label and/or investigational uses of drugs**
- **ODYSSEY OUTCOMES was sponsored by Sanofi Aventis and Regeneron**

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Just published 3 days ago in *NEJM*…

ORIGINAL ARTICLE

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

G.G. Schwartz, P.G. Steg, M. Szarek, D.L. Bhatt, V.A. Bittner, R. Diaz, J.M. Edelberg, S.G. Goodman, C. Hanotin, R.A. Harrington, J.W. Jukema, G. Lecorps, K.W. Mahaffey, A. Moryusef, R. Pordy, K. Quintero, M.T. Roe, W.J. Sasiela, J.-F. Tamby, P. Tricoci, H.D. White, and A.M. Zeiher, for the ODYSSEY OUTCOMES Committees and Investigators*

Schwartz et al. NEJM Nov 7, 2018 doi: 10.1056/NEJMoa1801174

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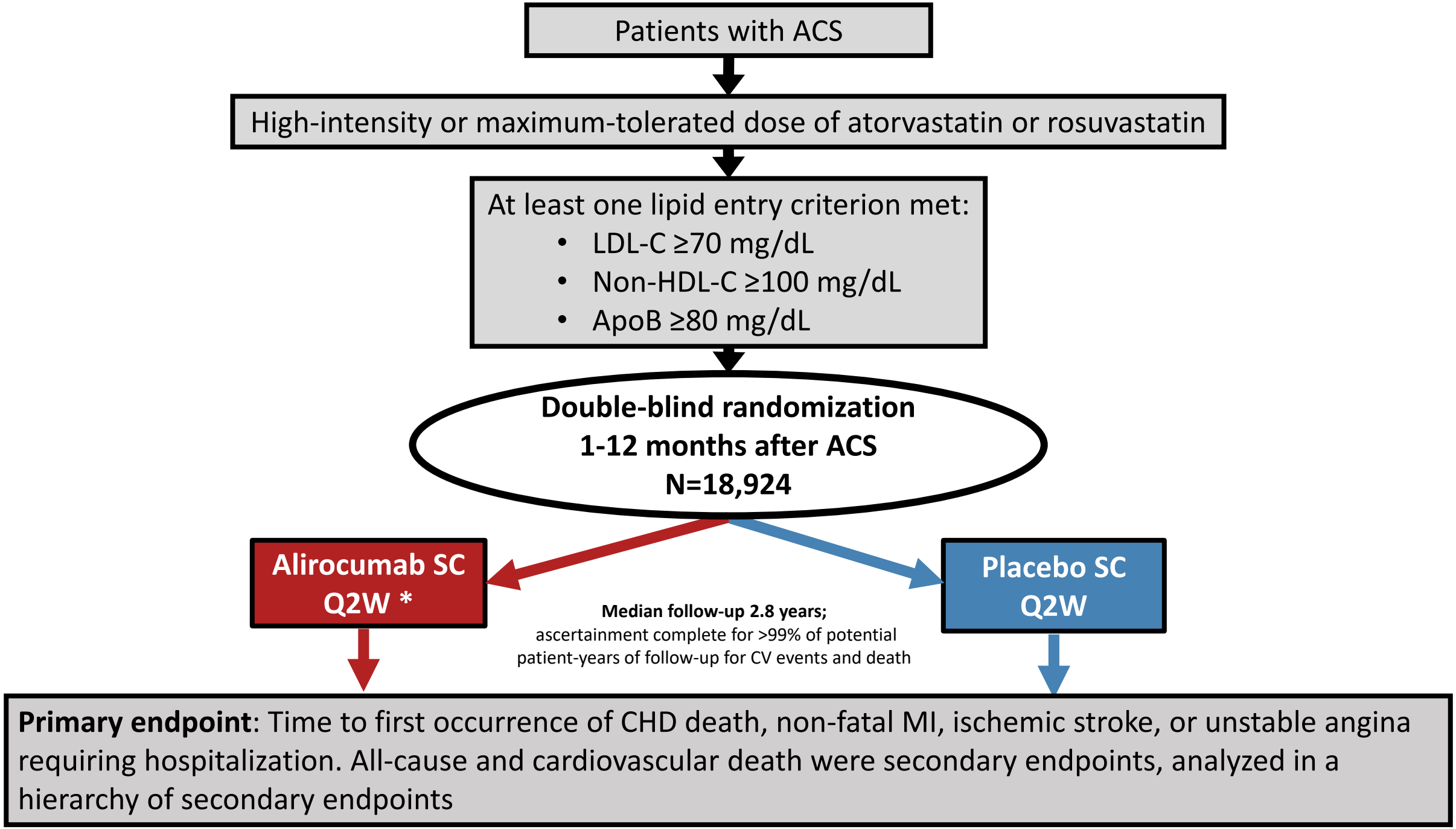
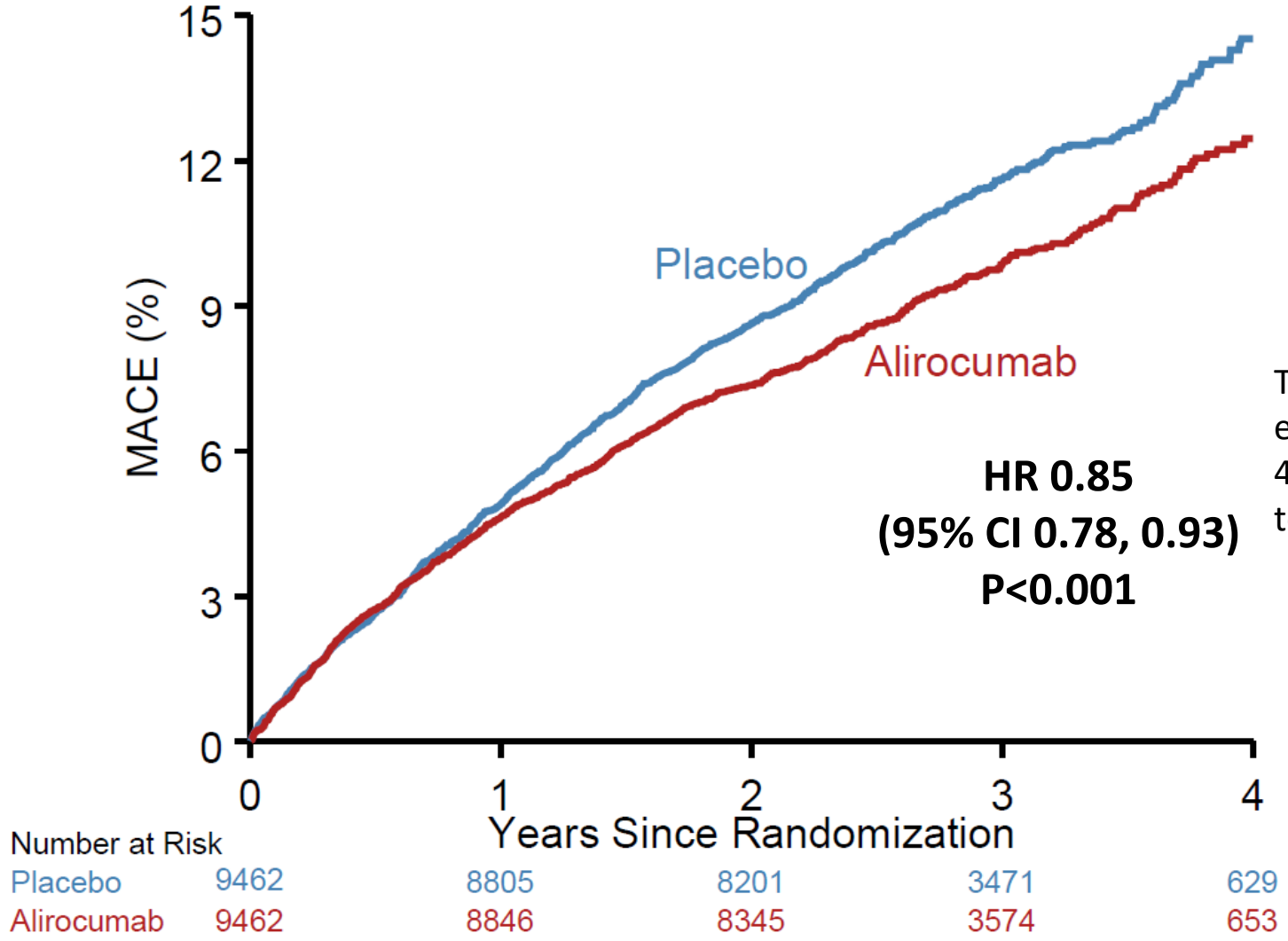


*Blinded adjustment of alirocumab dose to target achieved LDL-C 25-50 mg/dL and avoid sustained levels <15 mg/dL

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

To prevent one primary endpoint event would require 49 (95% CI 28 to 164) patients to be treated for 4 years

Schwartz et al. NEJM Nov 7, 2018 doi: 10.1056/NEJMoa1801174

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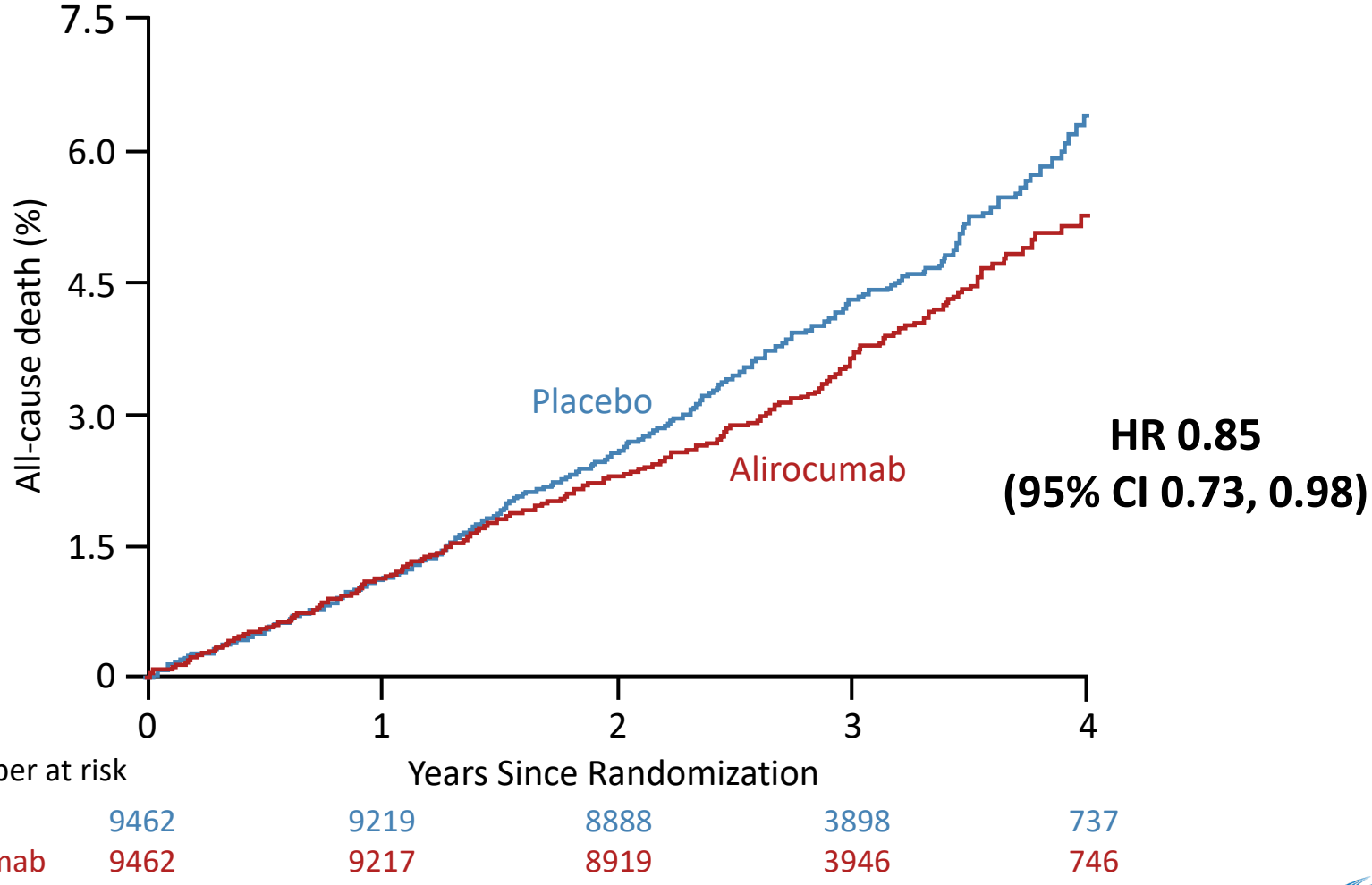
All-Cause Death



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Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

Schwartz et al. NEJM Nov 7, 2018 doi: 10.1056/NEJMoa1801174

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Study Objective

To conduct a trial-based cost effectiveness analysis of alirocumab in patients with elevated LDL-C despite a background of high-intensity or maximally tolerated statin therapy from the perspective of a US payer

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Methods: Cost Data

- Diagnosis-related group (DRG) cost based on Medicare
  - Weighted by national frequency for each CV event type
  - Adjusted rates published by the Centers for Medicare and Medicaid Services (CMS) were assumed for the study
  - Adjusted for commercial rates to account for those <65 years of age
- Cost was applied to CV death and recurrent non-fatal events: MI, ischemic stroke, coronary revascularization, and unstable angina requiring hospitalization
- Follow-up costs after acute events were not included in this analysis

Costs From Reimbursement Rates*†

Events	CV Event Costs†
CV Death	$20,225
Non-fatal MI (without revascularization)	$18,862
Non-fatal ischemic stroke	$12,617
Ischemia-driven coronary revascularization or unstable angina	$39,531

* Cost of concomitant medications (e.g., statins) not included

† Cost from Medicare reimbursement rates were adjusted to 2018 dollars and to account for subjects <65 years of age, an adjustment factor (1.88 x) was used to reflect a commercial reimbursement rate (73.5% of ODYSSEY OUTCOMES patients were ≤65 years of age). All CV event costs were defined with ICD-10 and DRG costs based on the ODYSSEY OUTCOMES protocol definitions and validated by external coding experts.

CMS: https://data.cms.gov/Medicare-Inpatient/National-Summary-of-Inpatient-Charge-Data-by-Medic/efwk-h4x3/data;
CMS: Inpatient Prospective Payment System Provider Summary for All Diagnosis-Related Groups - FY2015. https://data.cms.gov/Medicare-Inpatient/Inpatient-Prospective-Payment-System-IPPS-Provider/w2du-it53. Published October 31, 2017. Accessed October 16, 2018;
CMS: Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2018 Rates; Final Rule. Department of Health and Human Services, CMS, Federal Register. Vol. 82, No. 155, Page 38178. Monday, August 14, 2017.
Congressional Budget Office, Mareda and Nelson. Annual Research Meeting Academy Health, Presentation, June 2017

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Methods

- Extrapolated long-term survival probability, as is standard in C-E analyses
  - Estimates were based on Nelson et al,[1] where survival is extrapolated based on age-based mortality rates observed in the placebo arm of the trial
  - We applied observed hazard ratio (HR) to the extrapolated survival curve for placebo arm to estimate long-term survival for the alirocumab arm
- Health-related quality of life (QOL)
  - Baseline utility and CV event disutility weights were estimated from within the trial using EQ-5D
- Treatment effect
  - HRs for all-cause death
  - Event rates for non-fatal recurrent events

[1] Nelson CL, Sun JL, Tsiatis AA, Mark DB. Stat Med. 2008 Nov 20;27:5525-55.

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Analyses

- Base case
  - Overall intention-to-treat (ITT) population
- Subgroup analyses
  - Patients with LDL-C ≥100 mg/dL at baseline
  - Patients with LDL-C <100 mg/dL at baseline

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All-Cause Mortality Rates and Hazard Ratios

		Overall
ITT	Alirocumab (per 100 patient years)	1.24
	Placebo (per 100 patient years)	1.46
	Hazard ratio	**0.85**
LDL-C ≥100 mg/dL	Alirocumab (per 100 patient years)	1.41
	Placebo (per 100 patient years)	2.02
	Hazard ratio	**0.71**
LDL-C <100 mg/dL	Alirocumab (per 100 patient years)	1.16
	Placebo (per 100 patient years)	1.22
	Hazard ratio	**0.95**

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Cardiovascular Event Rates for ITT Population

ITT population	Annual event rate for alirocumab per 100 patient-years	Annual event rate for placebo per 100 patient-years
CV death	0.89	1.01
Non-fatal MI	3.20	3.69
Non-fatal ischemic stroke	0.44	0.62
Unstable angina	0.14	0.24
Ischemia-driven coronary revascularization	3.19	3.70

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Value-Based Price

		Annual price of alirocumab to be cost effective
Scenario	Population	**$100,000/QALY**
Base case	ITT	**$6,319**

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Value-Based Price

		Annual price of alirocumab to be cost effective
Scenario	Population	**$100,000/QALY**
Base case	ITT	**$6,319**
Baseline LDL-C	≥100 mg/dL	$13,357

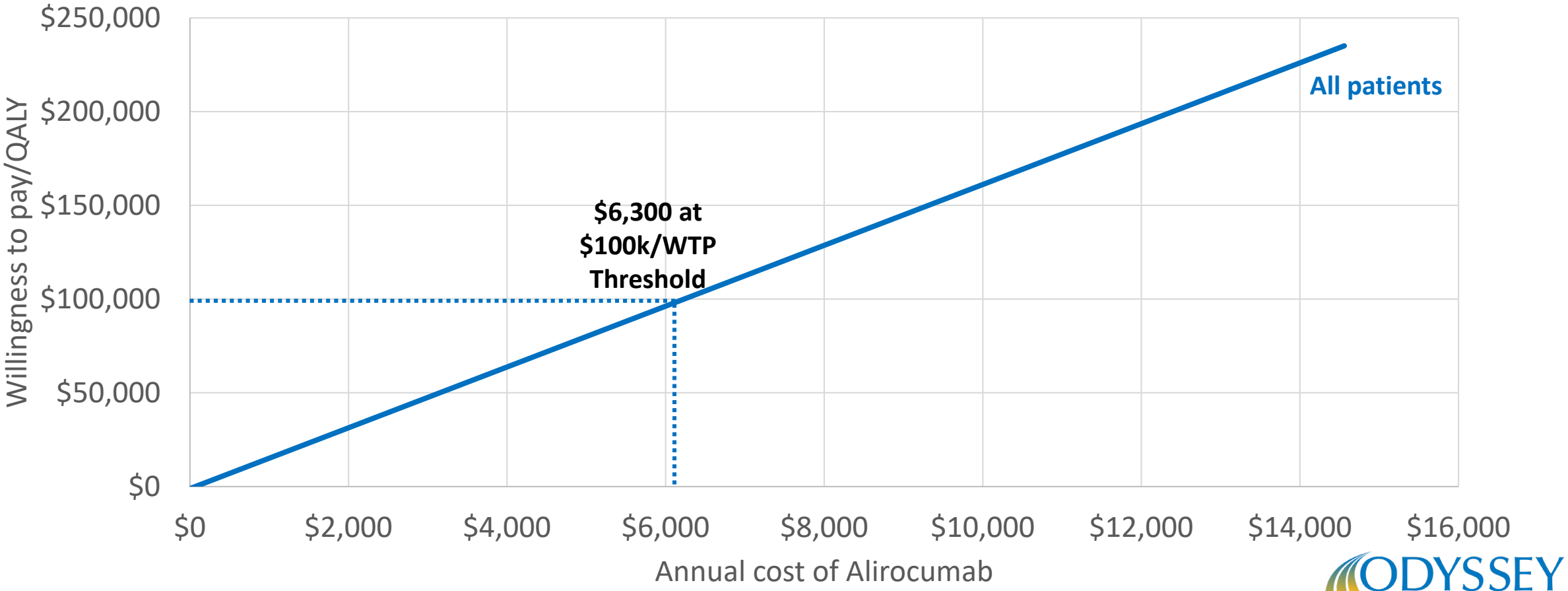
ODYSSEY OUTCOMES

Value-Based Price

		Annual price of alirocumab to be cost effective
Scenario	Population	**$100,000/QALY**
Base case	ITT	**$6,319**
Baseline LDL-C	≥100 mg/dL	$13,357
Baseline LDL-C	<100 mg/dL	$2,083

ODYSSEY OUTCOMES

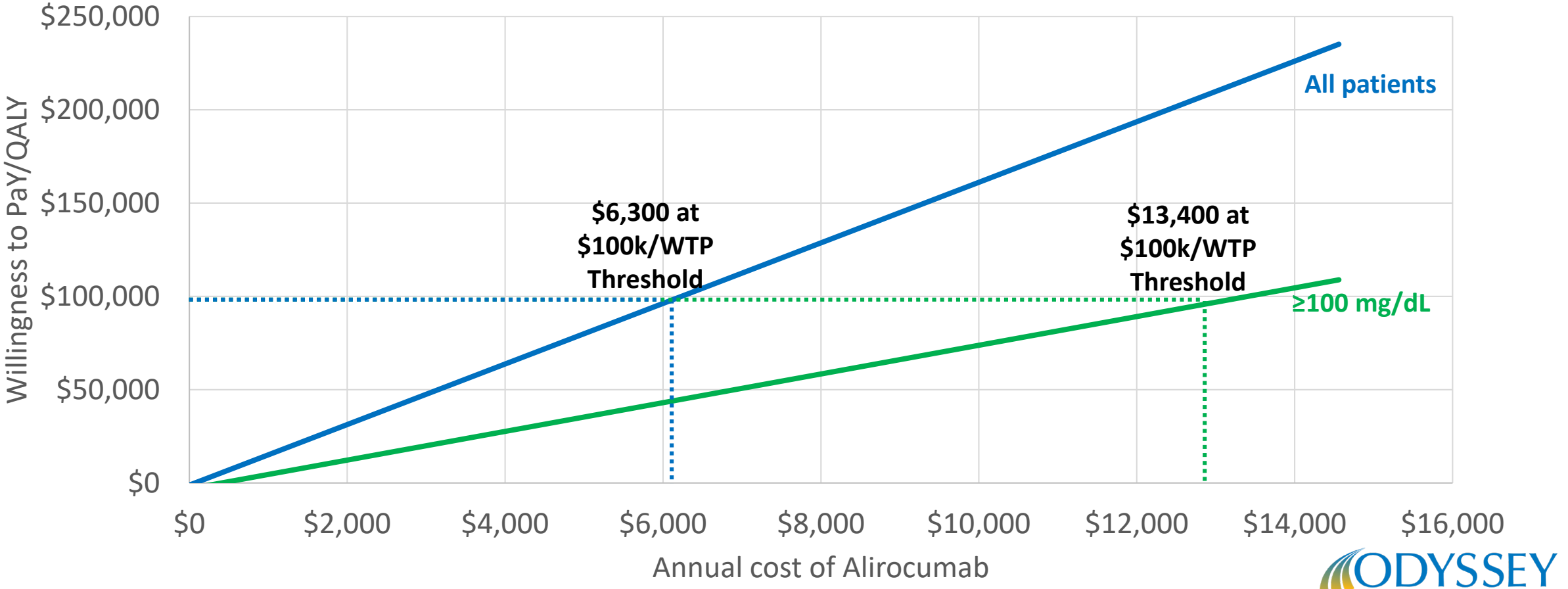
Varying the Cost of Alirocumab



ODYSSEY OUTCOMES

Varying the Cost of Alirocumab

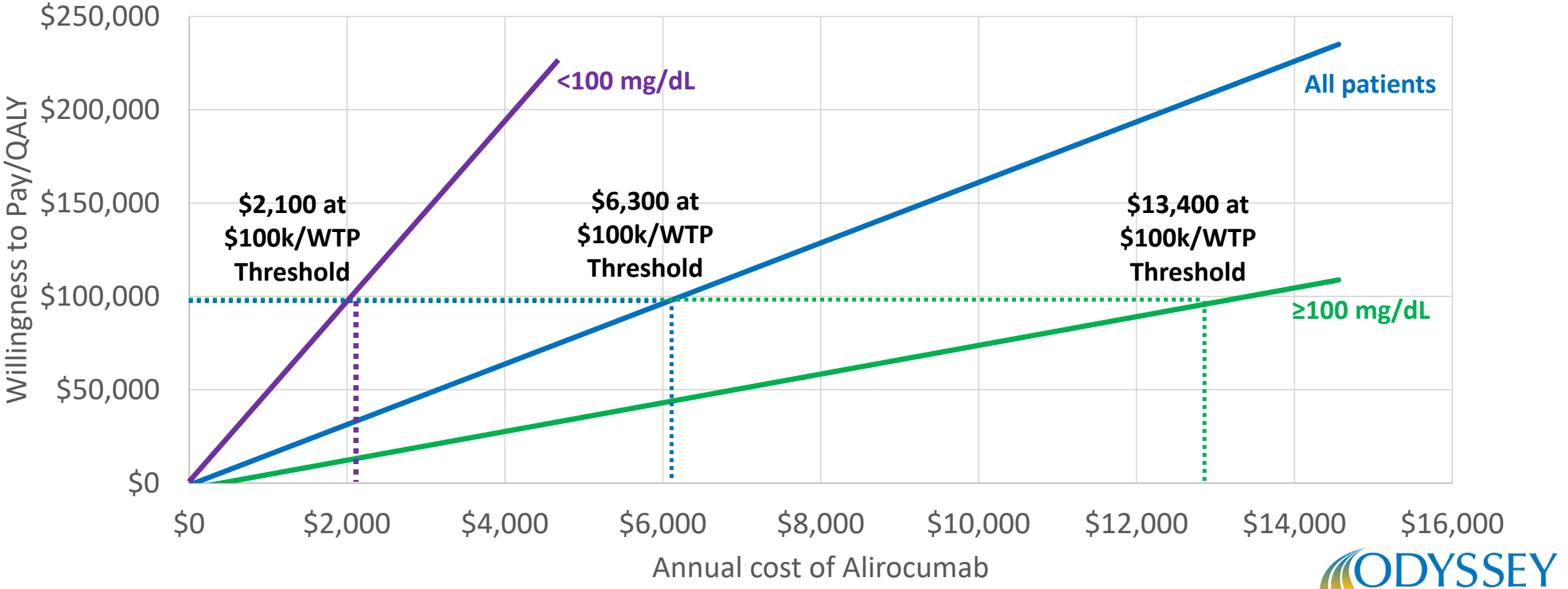
At any level of willingness to pay, cost-effectiveness is greater in patients with baseline LDL-C values ≥100 mg/dL relative to the overall ITT population



ODYSSEY OUTCOMES

Varying the Cost of Alirocumab

At any level of willingness to pay, cost-effectiveness is lesser in patients with baseline LDL-C values <100 mg/dL relative to the overall ITT population



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Strengths

- **Trial-based economic model** that leverages patient-level data from ODYSSEY OUTCOMES to inform the analysis with fewer assumptions compared with cohort-based Markov models
- All-cause death and total events data from the trial were used

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Limitations

- Modeling done with all-cause mortality, which was nominally significant, i.e., not by the prespecified hierarchical testing of secondary endpoints
- Country-specific costs were not used – US costs were applied to the global population
- Cost only includes event cost based on US reimbursement rates – no follow-up costs were included (results are conservative, in this regard)
- Factors other than high LDL-C, e.g., diabetes, may identify additional patients for whom treatment with alirocumab has favorable cost effectiveness

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Conclusion

- In the overall ODYSSEY OUTCOMES population, alirocumab was cost effective at a price up to **$6,319** per year at the $100,000 willingness to pay threshold
- The higher the baseline LDL-C, the higher the value of alirocumab appeared to be
- Based on both absolute clinical benefit and cost-effectiveness, alirocumab may offer good value in patients with a history of ACS and LDL-C ≥100 mg/dL despite maximally tolerated statin therapy

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Back up

Cost/QALY Calculation

- Lifetime cost and quality adjusted life years (QALYs) accrued for each treatment group were estimated
- Cost effectiveness was measured as the incremental cost effectiveness ratio (ICER), defined as

$$\frac{\text{Cost}_{\text{alirocumab}} - \text{Cost}_{\text{placebo}}}{\text{QALYs}_{\text{alirocumab}} - \text{QALYs}_{\text{placebo}}}$$

- We estimated the annual cost of alirocumab to be cost effective across commonly used willingness to pay thresholds
- Cost and QALYs were discounted at 3% per year

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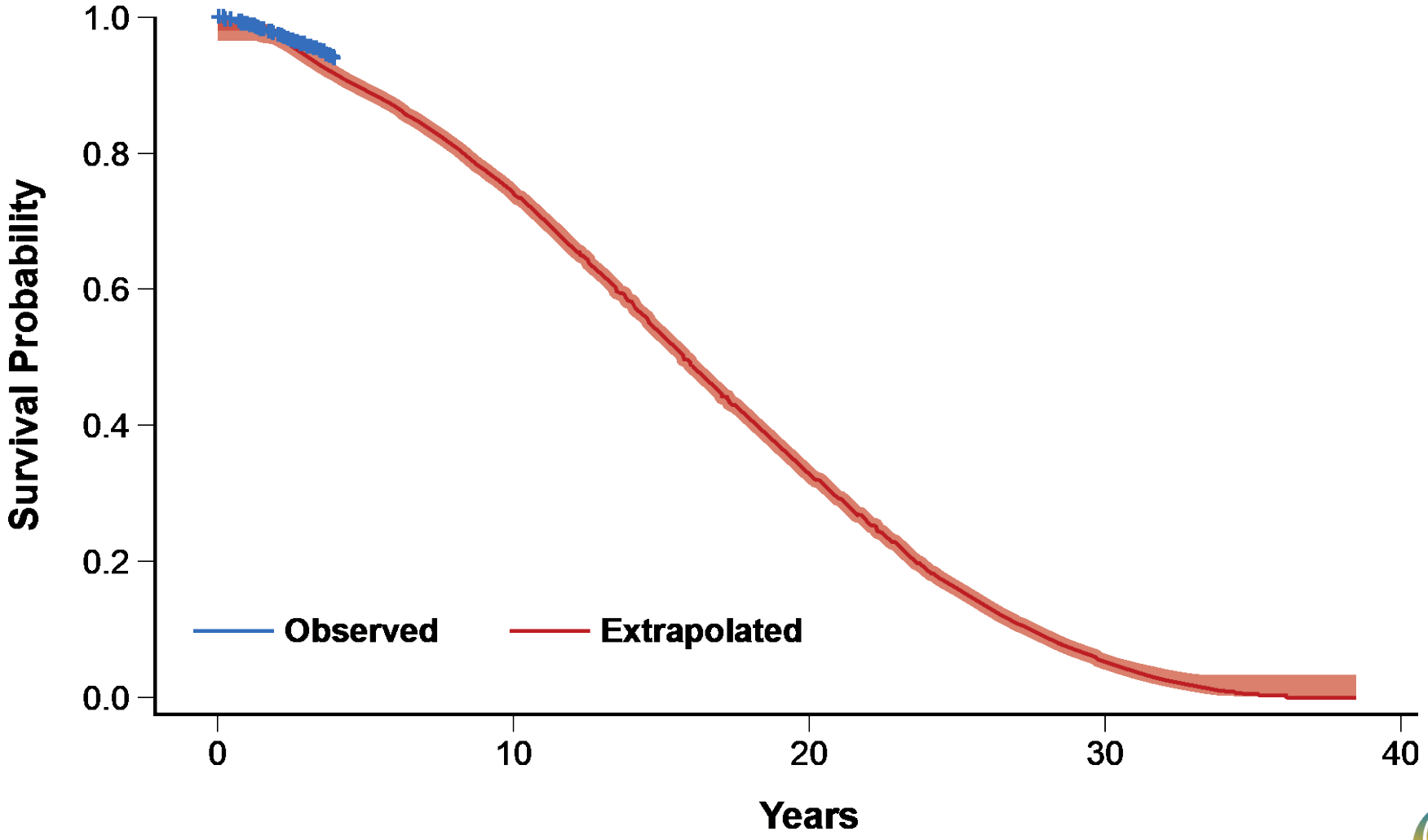
Survival Curves (95% Confidence Bands) in Placebo Group*



* Extrapolation based on methodology from Nelson CL, Sun JL, Tsiatis AA, Mark DB. Stat Med. 2008;27:5525-55.

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Interpreting Extrapolated Survival Curve

- The observed survival represents
  - Varying follow-up from 5 days to 4 years
- The extrapolated survival for the first 4 years
  - Followed-up all subjects for 4 years
    - Resulting in a more aged population
  - Higher risk of mortality in older subjects
    - Resulting in higher cumulative mortality rate
- The separation of the extrapolated and observed survival curves
  - Due to aged population as a result of continuing following-up

Value-Based Price

		Annual price of alirocumab to be cost effective at varying willingness to pay thresholds		
Scenario	Population	$50,000/QALY	**$100,000/QALY**	$150,000/QALY
Base case	ITT	$3,293	**$6,319**	$9,346
Baseline LDL-C	≥100 mg/dL	$6,910	**$13,357**	$19,805
Baseline LDL-C	<100 mg/dL	$1,139	**$2,083**	$3,028
Stratified HR (< 1 year/ ≥ 1 year)	ITT	$4,483	**$8,600**	$12,717

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