Post-licensure safety of an adjuvanted hepatitis B vaccine:

Final results of the HEPLISAV-B acute myocardial infarction study

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Disclosure/Conflicts of interest

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Background

Heplisav-B®

2 doses (0, 1 month)

Novel adjuvant – TLR 9 agonist

Peak seroprotection – 95.4%

Numerical “imbalance” in acute myocardial infarction (AMI) in a single clinical trial

Engerix-B®

3 doses (0, 1, 6 months)

Alum adjuvant

Peak seroprotection – 81.3%

No known safety risk

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Objective

Compare occurrence of AMI in recipients of Heplisav-B and recipients of Engerix-B

Real-world post-licensure safety study

Requirement as part of vaccine licensure

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Licensure and recommended timeline

July 2017	FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) votes 12 to 1 that the safety data support licensure
August 2017	Original Prescription Drug User Fee Act (PDUFA) date (extended to November 2017)
November 2017	Biologics License Application (BLA) is approved
February 2018	Advisory Committee on Immunization Practices (ACIP) recommends new hepatitis B vaccine for use in adults
April 2018	ACIP recommendation is published in *Morbidity and Mortality Weekly Report*
August 2018	Vaccine first used at Kaiser Permanente Southern California

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Study setting

Kaiser Permanente Southern California (KPSC)

- Large, diverse integrated health care system
- 4.7 million members
- 150+ languages
- 15 medical centers (hospitals + 231 medical offices)
- 4.6 million vaccinations administered in 2019

Kaiser Permanente HealthConnect®

- Comprehensive electronic health record system
- Ideal system in place to identify who can benefit from vaccination
- Hep B vaccination alert for patients with diabetes

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Study design

Non-randomized cluster design

- Heplisav-B became only available hepatitis B vaccine in family and internal medicine departments at 7 medical centers
- Other 8 medical centers continued to use Engerix-B in family and internal medicine departments
- Selection of medical centers primarily based on operational considerations

Routine vaccine administration over 14 months (Aug 2018 - Oct 2019)

Individuals passively followed through electronic health records for 13 months after first dose during study accrual period (index dose)

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Outcome

Primary outcome

- Type 1 AMI (definite + probable)
- First occurrence during 13-month follow-up after index date

Potential AMI events identified by ICD-10-CM diagnosis codes from inpatient care or emergency department visit with same or next day death

Events from hospitals outside KPSC captured from claims records

All events adjudicated by cardiologist reviewers masked to vaccine group

Results reviewed by independent data monitoring committee

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Adjudication process

Cardiologist reviewers used Fourth Universal Definition of Myocardial Infarction to classify potential AMI events as one of the following:

- Definite AMI
- Probable AMI
- Insufficient information
- Not AMI

AMI Type (for definite or probable AMI events)

Cases with disagreement from two cardiologist reviewers went to third reviewer as tie-breaker

- Cases with disagreement from all three cardiologist reviewers considered indeterminate

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Analysis

Non-inferiority study design

- Rule out H_0: hazard ratio (HR) ≥ 2.0

Cox proportional hazards model with inverse probability of treatment weighting (IPTW)

Covariates considered:

- Socio-demographics
- Diabetes in prior year
- AMI in prior year
- Cardiovascular disease risk factors and medications in prior year
- Comorbidities in prior year
- Healthcare utilization in prior year
- Receipt of concomitant vaccines

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Additional analyses

Sensitivity analyses performed using alternative methods:

- Propensity score-adjusted and -stratified Cox proportional hazards model
- Multivariable Cox proportional hazards regression model

Additional sensitivity analyses performed for:

- All types of AMI events
- Confirmed type 1 AMI + indeterminate events

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Additional analyses

Subgroup analyses were also performed for individuals with:

- Age <50 years at index dose
- Age ≥50 years at index dose
- Diabetes in the year prior to index dose
- Hypertension in the year prior to index dose
- Receipt of concomitant vaccination
- Index dose as first hepatitis B vaccination
- Index dose as subsequent hepatitis B vaccination

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Results

Vaccine accrual by dose

	Heplisav-B N (%)	Engerix-B N (%)	Total N (%)
Recipients with one dose	16,641 (53.4)	20,825 (54.2)	37,466 (53.8)
Recipients with two doses	14,292 (45.8)	9,951 (25.9)	24,243 (34.8)
Recipients with three doses	250 (0.8)	7,666 (19.9)	7,916 (11.4)
Total number of recipients	**31,183 (100)**	**38,442 (100)**	**69,625 (100)**

*Accrual of index dose from Aug 2018 – Oct 2019; subsequent dose accrued through Nov 2020.

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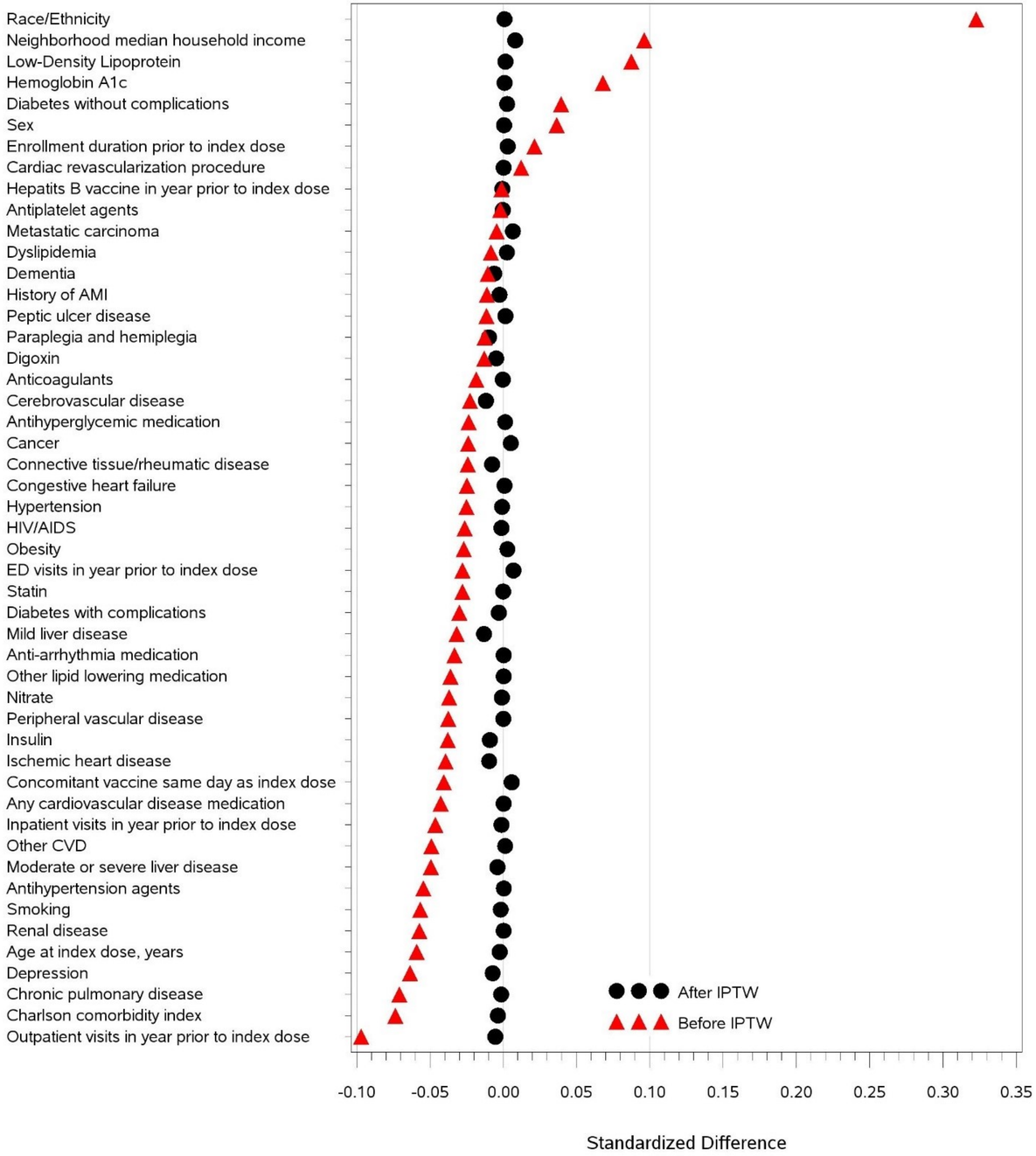
Standardized differences comparing characteristics for Heplisav-B and Engerix-B recipients before and after inverse probability of treatment weighting (IPTW)



AMI rates

	Heplisav-B (N = 31,183)	Engerix-B* (N = 38,442)	Total (N = 69,625)
Number of potential events reviewed	74	128	202
Number of type 1 AMI events confirmed	52 (70.3%)	71 (55.5%)	123 (60.9%)
Follow-up time (person-years)	31,139	38,200	69,339
Rate per 1000 person-years	1.67	1.86	1.77

*In Engerix-B group, a higher proportion of events came from claims, and a lower proportion of claims were adjudicated as AMI.
*Background AMI rate among KPSC adults in 2020 is 1.74 per 1000 person-years.

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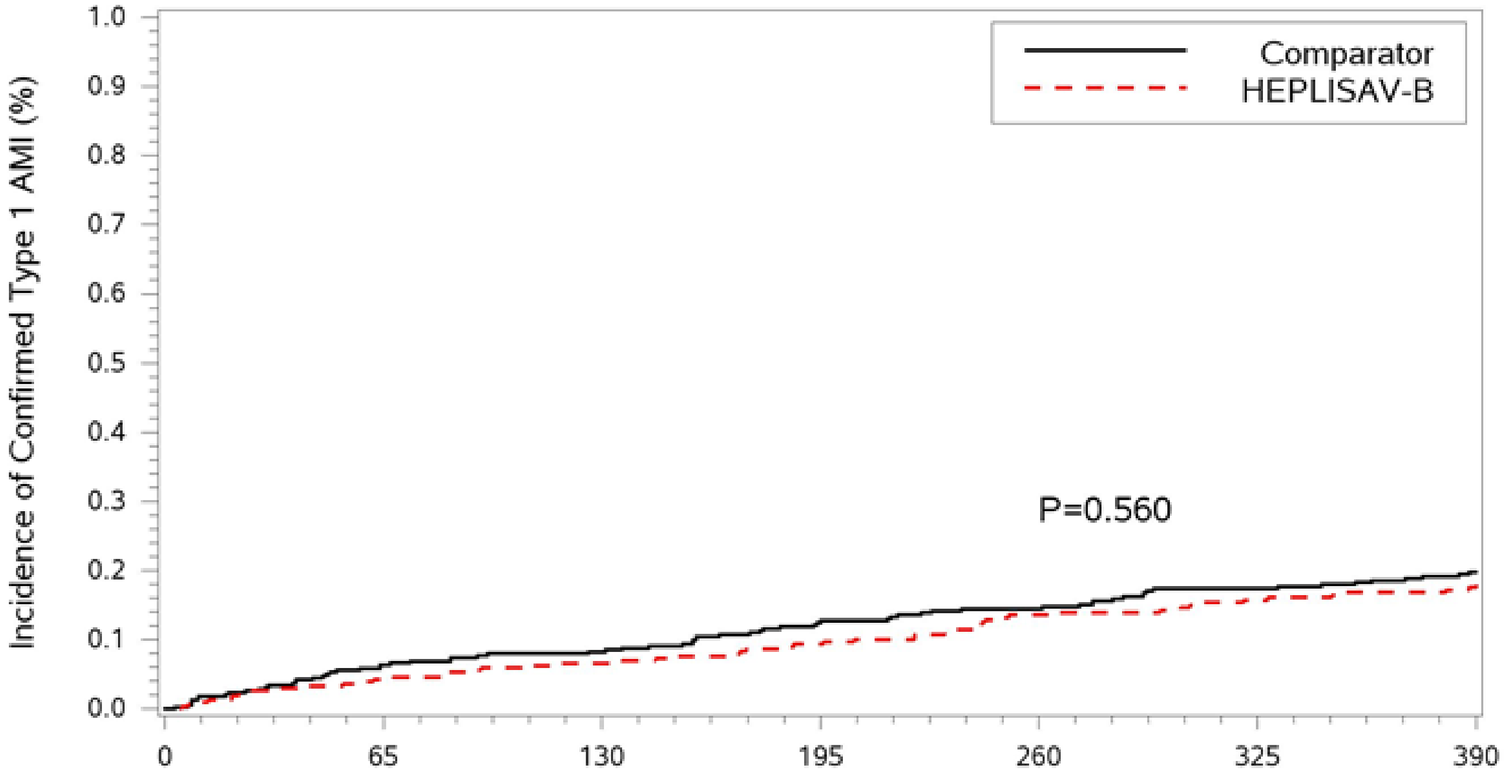
Cumulative incidence



Group	Number at Risk						
Comparator	38442	37310	36214	35220	34323	33520	32802
HEPLISAV-B	31183	30267	29434	28733	28121	27418	26820

Comparator: Engerix-B

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Results: HR for confirmed type 1 AMI events, Heplisav-B vs. Engerix-B

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Cox model with IPTW	0.90 (0.63-1.29)	0.92 (0.63-1.32)
Sensitivity analyses		
Multivariable-adjusted Cox model*		0.96 (0.67-1.39)
Propensity score-adjusted Cox model		0.95 (0.66-1.36)
Propensity score-stratified Cox model		0.95 (0.66-1.37)

*Adjusted for age, sex, race/ethnicity, history of AMI, Charlson score, hemoglobin A1c, diabetes, renal disease, ischemic heart disease, and nitrate use.

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Results: HR for all types of AMI and indeterminate events, Heplisav-B vs. Engerix-B

Cox model with IPTW for all types of AMI events	0.84 (0.62-1.15)	0.86 (0.63-1.19)
Cox model with IPTW for confirmed type 1 AMI + indeterminate events	0.82 (0.58-1.16)	0.83 (0.58-1.19)

Subgroup analysis results: HR for confirmed type 1 AMI events, Heplisav-B vs. Engerix-B

	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Age <50 years at index dose	0.89 (0.42-1.88)	0.81 (0.38-1.76)
Age ≥50 at index dose	0.93 (0.62-1.40)	0.99 (0.65-1.49)
Diabetes in the year prior to index dose	0.96 (0.65-1.43)	1.00 (0.66-1.50)
Hypertension in the year prior to index dose	0.83 (0.51-1.33)	0.91 (0.57-1.47)
Concomitant vaccine recipients	0.84 (0.50-1.43)	0.86 (0.51-1.45)
Index dose as first hepatitis B vaccination	0.95 (0.64-1.41)	0.98 (0.66-1.46)
Index dose as subsequent hepatitis B vaccination	0.70 (0.29-1.67)	0.71 (0.29-1.76)

*Cox model with IPTW

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Strengths and limitations

Observational study: Potential for measured and unmeasured confounding

- Considered many sociodemographic and clinical covariates
- Conducted multiple sensitivity and subgroup analyses

Misclassification of exposure

- Vaccine doses were validated

Misclassification of outcome

- More events from claims (outside KPSC health system) in Engerix-B group, with lower proportion adjudicated as definite or probable AMI

Generalizability to other patient populations

- Large, diverse population

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Conclusion

There is no evidence of an increased risk of AMI associated with vaccination with Heplisav-B compared to Engerix-B.

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