Comparative Effectiveness of Long-Acting Lipoglycopeptides vs Standard of Care in Serious Bacterial Infections

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**Key Points:**

**Question:** What is the comparative effectiveness of long acting lipoglycopeptides (laLGP) vs. standard of care antibiotics as a step-down treatment of serious gram-positive bacterial infections?

**Findings:** In this comparative effectiveness study using target trial emulation that included 42,736 adults in the United States, laLGPs showed similar results in a composite outcome of readmission, emergency room visit, or inpatient death within 90 days post-discharge compared to standard of care antibiotics.

**Meaning:** laLGPs are an effective alternative to standard of care antibiotics for the step down treatment of serious gram-positive bacterial infections.

**Abstract:**

**Importance:** Serious bacterial infections such as bacteremia, endocarditis, osteomyelitis, and septic arthritis, typically require prolonged intravenous antibiotics. Long-acting lipoglycopeptides (laLGPs), like dalbavancin and oritavancin, offer extended treatment intervals for gram positive infections which may benefit populations with barriers to traditional treatment, including persons who use drugs (PWUD).

**Objective:** To assess the effectiveness of laLGPs in managing serious bacterial infections in both PWUD and non-PWUD populations, compared with standard of care (SOC) antibiotics.

**Design:** Target trial emulation study

**Setting:** Data was extracted from the Cerner Real World Data platform (United States).

**Participants:** Individuals hospitalized and discharged for serious bacterial infections between October 2015 and October 2022.

**Intervention:** Receipt of laLGP (dalbavancin or oritavancin) vs. SOC antibiotics.

**Main outcome and measures:** Our primary outcome measure was a composite outcome that included readmission, emergency room visit, and inpatient death or discharge to hospice within 90 days post-discharge from the index admission. We stratified analyses by status as a person who uses drugs (PWUD) or not (non-PWUD). We used clone censor weighting to emulate a per protocol analysis. We computed hazard ratios (HR) of time to the composite event and calculated 95% confidence intervals using bootstrapping.

**Results:** Among 42,121 included individuals, median age was 61 years (IQR 47-73 years), 41% were female, and 12% were PWUD. laLGPs were prescribed in 2.1% individuals. There was no statistically significant difference in the composite outcome between the laLGP group and the standard of care group in both PWUD HR 1.01, 95% CI 0.88-1.13) and non-PWUD (HR 0.93, 95% CI 0.86-1.00).

**Conclusion:** In this target trial emulation study of laLGPs vs SOC, laLGPs were effective as step down treatment of serious gram-positive bacterial infections, offering comparable outcomes to SOC antibiotics in both PWUD and non-PWUD populations. Clinicians may consider laLGPs as alternatives step-down options to SOC antibiotics for the treatment of serious gram-positive bacterial infections.

**Introduction**

Serious bacterial infections, such as bloodstream infections (BSI), endocarditis, septic arthritis, osteomyelitis, and pyomyositis, have increased in the United States 1-4. Serious bacterial infections are often treated with intravenous or oral antibiotics 5 for at least four weeks. Intravenous antibiotics can be administered as outpatient parenteral antibiotic therapy (OPAT) through short-term vascular catheters, though frequent laboratory monitoring and challenges with adherence may be prohibitive for many patients 6. Providers face significant barriers in offering OPAT to people who use drugs (PWUD) 7-10, including the inability to get home health care agencies to care for such patients due to stigma. The lack of OPAT for PWUD results in prolonged hospitalizations, higher rates of patient-directed discharge, premature treatment discontinuation, and mortality 11,12. Long-acting lipoglycopeptides (laLGPs), like dalbavancin and oritavancin, offer promising new treatment options for both PWUD and non-PWUD with these infections.

Dalbavancin and oritavancin, with half-lives of 346 and 393 hours respectively, show promise in treating serious bacterial infections 13-15. Therapeutic concentrations of laLGPs may remain above minimum inhibitory concentrations for many gram-positive organisms in serum and deep tissues for up to 8 weeks 16. Although currently approved only for the treatment of acute bacterial skin and skin structure infections, several case series highlight the use of laLGPs for serious bacterial infections 17-24. Limitations of the published evidence relate primarily to study design, including small sample size, single center, lack of a comparison group, and lack of randomization.

LaLGPs have the potential to serve as step-down treatments and alternatives to daily inpatient intravenous antibiotics, OPAT, or oral antibiotics 17,25. Our objective was to evaluate the off-label use of laLGPs for serious bacterial infections among people who do and do not use drugs in a large real world clinical database comparing laLGPs to other treatment regimens. We hypothesized that individuals receiving laLGPs would have similar or better outcomes to those receiving standard of care antibiotics.

**Methods**

Specification of the target trial

We specified a randomized pragmatic target trial to evaluate the efficacy of laLGPs compared to SOC antibiotics in adults hospitalized with a serious bacterial infection that survived until discharge on reducing post-discharge outcomes at 90 days. Supplemental Table 1 summarizes the protocol components. We emulated the target trial using observational data from the Cerner Real World Data platform, a national (United States) de-identified big data source of multicenter electronic health records containing records of over 100 million patients and 1.5 billion encounters 26. We adhered to RECORD guidelines for studies using observational routinely-collected data 27. This study was deemed exempt from ethics review by the institutional review board at the University of California, Los Angeles. The current analysis was performed from July 2023 to February 2025.

Study population

We included individuals in the emulated trial that met the following criteria: 1) 18 year or older; 2) serious bacterial infections defined as a diagnosis of endocarditis, BSI, osteomyelitis, or septic arthritis; 3) time of diagnosis between 1 October 2015 and 1 October 2022; 4) diagnosis associated with an emergency room visit or hospital admission; and 5) received at least 7 days of antibiotics. We set 7 days as the minimum duration for antibiotic treatment to increase the likelihood that the included cases represented clinically relevant presentations of the specified infections. We used the first episode of the inclusion diagnosis in the analysis as the index encounter and patients were only included once in the analysis. We chose the date range beginning 1 October 2015, as this was the earliest date laLGP were prescribed, and ending 1 October 2022 to allow for at least 90 days of follow-up for all individuals.

We excluded individuals that: 1) had a concomitant central nervous system infection; 2) endocarditis requiring early surgical intervention (less than 10 days from initial diagnosis date); 3) presence of a prosthetic heart valve; 4) presence of a cardiac device (implantable cardiac defibrillator, pacemaker); 5) presence of a transplanted organ (kidney, heart, lung, liver, pancreas, bone marrow); 6) end-stage renal disease or dialysis; 7) end-stage liver disease; 8) died during the index hospitalization; 9) received terminal antibiotics not typical for a gram-positive infection (see Exposures subsection below); and 10) received laLGP prior to the day of discharge. To identify diagnostic conditions and procedures, we searched *International Classification of Diseases* (ICD) ninth and tenth revision, Systematized Nomenclature of Medicine (SNOMED) Clinical Terms, and Current Procedural Terminology (CPT) codes. Diagnostic and procedure codes and time frames used to identify these criteria are available in Supplemental Tables 2-4. We used dates for inclusion and exclusion criteria to ensure that the criteria were considered prior to the prescription of laLGPs.

Exposures

Our primary exposure variable was the prescription or not of a laLGP (dalbavancin or oritavanacin) for a serious bacterial infection. We considered individuals who were not prescribed a laLGP to be in the standard of care (SOC) group. SOC participants had to receive an antibiotic typical for a gram-positive infection as their end of therapy antibiotics. We defined antibiotics typical for use in gram-positive infection as monotherapy with vancomycin, daptomycin, oxacillin, nafcillin, dicloxacillin, flucloxacillin, cephalexin, cefazolin, cefadroxil, ceftaroline, trimethoprim/sulfamethoxazole (TMP/SMX), doxycycline, minocycline, linezolid, or tedizolid. Combinations with rifampin were also included. We used receipt of end of therapy antibiotics typical of gram-positive infections as a proxy for gram-positive infections due to the absence of microbiological data in the database.

Time zero was defined as the date of discharge. We set a grace period of 10 days from the date of discharge for individuals to receive the laLGP. We set the 10-day grace period as individuals may receive laLGPs outside of the initial hospitalization (e.g., at outpatient infusion centers or skilled nursing facilities) for billing and reimbursement purposes 28,29.

Stratums

We used previously published codes from the Centers for Disease Control and Prevention (CDC) and phenotyping libraries as well as keywords related to substance use to classify individuals as PWUD or non-PWUD 30-34. We classified individuals as PWUD if they had an ICD-9 or 10 code, or SNOMED code for substance use or a substance use disorder within a year prior to the date of their inclusion diagnosis. The codes we used to identify PWUD are given in Supplemental Table 5. We chose the broader term PWUD over people who inject drugs as prior work has shown that ICD codes misclassify injecting drug use 35.

Confounders

We included individual-level and facility-level variables documented prior to discharge as potential confounders. At the individual level, we included age at diagnosis, sex, race, ethnicity, insurance coverage, individual Elixhauser comorbidities, length of hospital admission, and type of discharge. Race was identified as U.S. census categories: White or Caucasian, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or mixed racial group. We grouped individuals who were not identified in the prior categories as other race. Due to small numbers, we also grouped those of American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or mixed racial group as Other race. We classified ethnicity as Hispanic/Latino or Not Hispanic/Latino. Ethnicity and race were used as documented in the database. We only included Elixhauser comorbidities codes from prior to the index hospitalization. For PWUD, additionally, we included covariates for any history of cocaine, opioid, or methamphetamine use or disorder, history of injection drug use, and history of receiving a medication for opioid use disorder (methadone or buprenorphine). At the facility level, we included facility location by 1-digit U.S. zip code, and bed size in 500 bed increments. Covariates with missing values were coded as missing and this category was used in analyses.

Outcomes

The primary outcome was a composite variable of clinical failure that included readmission, emergency room visit, or inpatient mortality or discharge to hospice within 90-days from the discharge date of the index encounter. All outcomes had to occur after the date of discharge of the initial index admission. A composite outcome was chosen to capture a broad range of clinically relevant events that may be indicative of treatment failure, consistent with prior infectious diseases research 36-38. We defined loss to follow-up as individuals who were right-censored within 90 days of discharge from the index hospitalization, meaning they had no recorded clinical encounters (e.g., outpatient visits, hospitalizations, or emergency department visits) after their last clinical encounter, and they did not meet any predefined endpoints within the 90-day post-discharge period.

Statistical analysis

We tabulated baseline covariates for those in the laLGP and SOC groups and used Fisher’s exact tests and t-tests to compare the groups within the PWUD and non-PWUD stratums. To estimate the effect of initiating laLGP therapy within 10 days of hospital discharge on 90‐day post‐discharge clinical outcomes within the target emulation trial framework 39, we applied the clone–censor–weighting (CCW) approach 40,41. The CCW approach mitigates immortal time bias by cloning individuals at baseline and censoring clones upon treatment deviation, and it minimizes selection bias by applying inverse probability weights to adjust for differences between censored and uncensored patients. In the CCW approach, each individual was cloned at the time of discharge into two treatment strategies: one in which laLGP therapy was initiated within the 10‐day grace period (laLGP group) and one in which standard-of-care (SOC) antibiotics were continued (SOC group). We censored laLGP clones on the day they did not receive laLGP therapy within the grace period or if they received SOC antibiotics during that time, whereas those in the SOC clone were censored on the day they received laLGP therapy. We estimated inverse probability of censoring weights (IPCW) at each time point using logistic regression models conditional on baseline covariates—including age, sex, race/ethnicity, insurance status, Elixhauser comorbidities, and facility characteristics. We truncated weights at the 99th percentile to limit extreme values and improve model stability. We then fitted weighted Cox proportional hazards models to estimate the effect on the composite outcome within 90 days of discharge. We reported hazard ratios (HRs) and the difference in restricted mean survival time (RMST) at 90 days. We derived confidence intervals for both indicators by performing 500 bootstrapped iterations, using the 2.5th and 97.5th percentiles of the bootstrap distribution as the lower and upper bounds, respectively. As sensitivity analyses, we fitted similar models with subsets by the qualifying diagnosis and comparing laLGP to vancomycin of cefazolin. We performed all analyses in R, version 4.0.2 within a Jupyter Notebook42.

**Results**

Cohort description

We identified a total of 59,886 individuals who met inclusion criteria. Reasons for exclusion (17,819 individuals, 30%) are detailed in Figure 1, with the most common reason being a history of end-stage renal disease (ESRD) (n=7,079, 12%). Of 41,881 individuals included in our analysis, 5,047 (12%) were identified as PWUD.

Trends in laLGP usage

In the entire sample, laLGPs were prescribed in 2.1% (n=825) of cases, including 4.8% (n=241) of PWUD and 1.6% (n=584) of non-PWUD. Dalbavancin was the most common laLGP prescribed (n=733; 89% of individuals that received laLGP). laLGPs were most used for treatment of osteomyelitis (n=454; 55%), followed by BSI (n=210; 25%), septic arthritis (n=157; 19%), and endocarditis (n=59; 6.4%). Some individuals had multiple inclusion diagnoses. Figure 2 shows trends over time by laLGP and inclusion diagnosis, and geographic use of laLGP in the United States.

Sample descriptions

Summary characteristics for the full sample of PWUD and non-PWUD are given in Table 1. For the PWUD group, the mean age was 45 years (SD = 14), 57% male, predominantly White or Caucasian (81%) and non-Hispanic or Latino (86%). In the non-PWUD group, the mean age was 61 years (SD = 17), 59% male, with majority White or Caucasian (78%), and non-Hispanic or Latino (82%). Missing data among PWUD was present for gender (<1%), race (5.8%), ethnicity (2.6%), insurance (21%), zip code (<1%), and bed size (<1%). Among non-PWUD, missing data was present for gender (<1%), race (7.6%), ethnicity (2.9%), insurance (21%), zip code (<1%), and hospital bed capacity (<1%). Among PWUD, there were no significant differences in the length of stay (laLGP: 12 days vs. SOC: 13 days, p = 0.40). PWUD in the laLGP group were more frequently discharged home (70% vs. 46%) and less frequently to nursing facilities or rehabilitation (2.9% vs. 21%, p < 0.001) than PWUD in the SOC group. Among non-PWUD, the laLGP group had similar lengths of stay (8 vs. 10 days, p = 0.21) and a higher likelihood of discharge home (82% vs. 60%, p < 0.001) and less likely to be discharged to a nursing home (6.2% vs 23%) than non-PWUD in the SOC group. There were no significant differences in loss to follow-up in the laLGP group compared to the SOC group in both PWUD (15% vs. 15%, p > 0.90) and non-PWUD (21% vs. 19%, p = 0.20). Among PWUD, the three most common terminal antibiotics in the SOC group were vancomycin (19%), cefazolin (17%), and cephalexin (12%). For non-PWUD, the three most common terminal antibiotics in the SOC group were cefazolin (20%), vancomycin (18%), and cephalexin (18%) (see Supplemental Tables 6 and 7 for full list).

Unadjusted outcomes

Unadjusted clinical outcomes for the full sample are given in Table 2. Among PWUD, 51% of individuals met the composite outcome of inpatient death, discharge to hospice, readmission or emergency room visit within 90 days after discharge. PWUD in the laLGP were less likely to meet the composite outcome within 90 days (44% vs. 52%, p = 0.02) and were less likely to be readmitted at 90 days than PWUD in the SOC group (26% vs 39%, p < 0.001). Among non-PWUD, 41% of individuals met the composite outcome within 90 days. Those in the non-PWUD laLGP group were less likely to meet the composite outcome (32% vs. 41%, p < 0.001) and were less likely to be readmitted (20% vs 31%, p < 0.001) than those in the non-PWUD SOC group.

Clone censor weighting analysis

Table 3 shows results of the bootstrapped Cox proportional hazards models. Among both PWUD and non-PWUD, there were no differences between the laLGP group and the SOC group in the composite outcome. In the non-PWUD stratum and individuals diagnosed with osteomyelitis, laLGP prescription had a protective effect on the composite outcome compared to the SOC group (HR 0.85, 95% CI 0.76 to 0.96). In analyses comparing specific antibiotics, non-PWUD in the laLGP group had a lower risk of the composite outcome compared to vancomycin (HR 0.84, 95% CI 0.76-0.92) and compared to cefazolin (HR 0.87, 95% CI 0.79 to 0.96). There were no significant differences in sub-analyses in the PWUD stratum.

**Discussion**

We examined utilization patterns and clinical effectiveness within a target trial emulation framework of laLGPs for the management of serious bacterial infections among PWUD and non-PWUD in a national database in the United States. We found individuals who received laLGPs had similar 90-day treatment outcomes compared to those who received standard of care antibiotics, and across individual serious bacterial infections. This is an encouraging finding for the off-label use of laLGPs and adds to the evidence base supporting the effectiveness of laLGPs among PWUD and non-PWUD 17-24.

Our study suggests clinicians are adopting laLGPs to treat serious bacterial infections, although overall use remains limited. We were not able to discern reasons for choosing a laLGP over other antimicrobials. Of note, in our study, patients with a history of mental health disorders, namely depression or psychosis, were more likely to receive laLGP than SOC. Clinicians may infer that those with mental health issues may be less likely to adhere to daily antibiotics and a laLGP may be ideal in this clinical situation. We also noted a higher percentage of serious bacterial infections were treated with laLGPs in the midwest and west regions compared with the pacific west and the northeast. This may suggest a preference for laLGPs in rural areas. OPAT (outpatient parenteral antimicrobial therapy) requires frequent laboratory monitoring and close nurse, pharmacist and physician follow up which may be more challenging in regions with limited access. As knowledge on oral antibiotics grows, research is needed to understand provider and patient preferences for managing serious bacterial infections and to educate prescribers on laLGP benefits and side effects 43-45.

Dalbavancin was the most frequently prescribed agent (89% of those receiving laLGPs), especially for treatment of osteomyelitis and BSI. This has important implications for our clinical effectiveness findings as the results may not extrapolate to oritavancin. Our study was unable to evaluate why there was a preference for dalbavancin over oritavancin. One notable factor early in the introduction of laLGP was the shorter infusion time of dalbavancin compared to oritavancin (30 minutes vs 3 hours). In March 2021, oritavancin was approved as a shorter infusion volume and time (1 hour) 46. Further studies are necessary to assess if this new formulation will increase usage of oritavancin.

Limitations

Several limitations should be considered. Our large retrospective multicenter dataset may have inherent biases like misclassification of diagnoses or incomplete records. Reliance on ICD codes for case identification could introduce coding errors or variability across healthcare facilities. Our classification of PWUD based solely on diagnostic codes might misrepresent the true population as providers may not necessarily diagnose substance use disorders or enter diagnostic codes into their electronic health record. There is a risk that a subset of patients classified as non-PWUD were PWUD. The lack of culture data required proxies for gram-positive infections, which may not accurately reflect the true microbiological profile. Despite adjusting for various covariates, residual confounding due to unmeasured or inaccurately measured factors remained possible. Antibiotic adherence and completion of SOC therapy were not directly measurable in this retrospective analysis. This limitation is particularly relevant for PWUD and those with other mental illness, among whom care pathways may vary significantly especially when directing their own discharge.

Conclusion

In this comparative effectiveness study of laLGPs, we observed that laLGPs were effective as step-down options in treating serious gram-positive bacterial infections, offering comparable outcomes to SOC antibiotics in both PWUD and non-PWUD populations. Our study highlighted utilization patterns and supported the clinical effectiveness of laLGPs in serious bacterial infections among a diverse patient population. While awaiting a randomized clinical trial,47 large national databases helped understand laLGPs’ efficacy, especially for off-label use among PWUD. Despite limitations, our findings suggested dalbavancin was an effective therapeutic option. Future research should compare patient and clinician preferences between intravenous treatments, laLGPs, and oral antibiotics, as well as the cost-effectiveness of each option. Clinically, laLGPs can be an effective alternative to standard antibiotic courses for serious bacterial infections.

**Declarations**

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**Data sharing statement:** All code used in the analysis were made available at http://www.github.com/davigood/cerner-lalgp. Given data use agreements, no data can be downloaded from the Cerner Real World Data platform. Other researchers may access the data and recreate the analysis with the code, but this may incur a cost.

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**Author Contributions:**

Goodman-Meza had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Goodman-Meza.

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Drafting of the manuscript: Goodman-Meza, Poimboeuf

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Statistical analysis: Goodman-Meza, Feng, Weiss

Obtained funding: Goodman-Meza

Supervision: Dore, Matthews.

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**Table 1. Baseline characteristics of patients admitted due to a serious bacterial infection stratified by drug use status and prescription of laLGP.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | PWUD | | | non-PWUD | | |
| **Characteristic** | **SOC** N = 4,806 | **laLGP**  N = 241 | **p-value2** | **SOC**  N = 36,436 | **laLGP**  N = 584 | **p-value2** |
| **Age, years, mean (SD)** | 46 (15) | 43 (13) | 0.02 | 62 (17) | 54 (17) | <0.001 |
| **Gender** |  |  | 0.70 |  |  | <0.001 |
| Male | 2,745 (57%) | 141 (59%) |  | 21,419 (59%) | 399 (68%) |  |
| Female | 2,059 (43%) | 100 (41%) |  | 14,999 (41%) | 185 (32%) |  |
| Unknown | 2 (<0.1%) | 0 (0%) |  | 18 (<0.1%) | 0 (0%) |  |
| **Race** |  |  | 0.13 |  |  | 0.06 |
| White or Caucasian | 3,901 (81%) | 197 (82%) |  | 28,336 (78%) | 471 (81%) |  |
| Black or African American | 435 (9.1%) | 14 (5.8%) |  | 3,707 (10%) | 45 (7.7%) |  |
| Other race1 | 190 (4.0%) | 15 (6.2%) |  | 1,641 (4.5%) | 18 (3.1%) |  |
| Unknown | 280 (5.8%) | 15 (6.2%) |  | 2,752 (7.6%) | 50 (8.6%) |  |
| **Ethnicity** |  |  | 0.80 |  |  | 0.70 |
| Not Hispanic or Latino | 4,141 (86%) | 204 (85%) |  | 29,839 (82%) | 484 (83%) |  |
| Hispanic or Latino | 543 (11%) | 30 (12%) |  | 5,553 (15%) | 82 (14%) |  |
| Unknown | 122 (2.5%) | 7 (2.9%) |  | 1,044 (2.9%) | 18 (3.1%) |  |
| **Insurance** |  |  | 0.10 |  |  | <0.001 |
| Medicaid | 2,102 (44%) | 104 (43%) |  | 6,092 (17%) | 144 (25%) |  |
| Medicare | 817 (17%) | 28 (12%) |  | 14,343 (39%) | 160 (27%) |  |
| Commercial insurance | 325 (6.8%) | 15 (6.2%) |  | 5,841 (16%) | 88 (15%) |  |
| Other | 573 (12%) | 38 (16%) |  | 2,598 (7.1%) | 91 (16%) |  |
| Unknown | 989 (21%) | 56 (23%) |  | 7,562 (21%) | 101 (17%) |  |
| **Comorbidities** |  |  |  |  |  |  |
| Alcohol abuse | 478 (9.9%) | 33 (14%) | 0.06 | 1,298 (3.6%) | 21 (3.6%) | >0.9 |
| Blood loss anemia | 60 (1.2%) | 1 (0.4%) | 0.40 | 362 (1.0%) | 9 (1.5%) | 0.20 |
| Chronic peptic ulcer disease | 51 (1.1%) | 4 (1.7%) | 0.30 | 336 (0.9%) | 5 (0.9%) | 0.90 |
| Chronic pulmonary disease | 851 (18%) | 43 (18%) | >0.9 | 5,226 (14%) | 88 (15%) | 0.60 |
| Coagulation deficiency | 233 (4.8%) | 11 (4.6%) | 0.80 | 1,748 (4.8%) | 27 (4.6%) | 0.80 |
| Congestive heart failure | 363 (7.6%) | 17 (7.1%) | 0.80 | 3,780 (10%) | 48 (8.2%) | 0.090 |
| Deficiency anemias | 984 (20%) | 62 (26%) | 0.05 | 7,068 (19%) | 119 (20%) | 0.6 |
| Depression | 951 (20%) | 65 (27%) | 0.007 | 3,390 (9.3%) | 86 (15%) | <0.001 |
| Diabetes with chronic complications | 589 (12%) | 42 (17%) | 0.02 | 6,671 (18%) | 160 (27%) | <0.001 |
| Diabetes without chronic complications | 864 (18%) | 47 (20%) | 0.50 | 10,649 (29%) | 203 (35%) | 0.004 |
| Fluid and electrolyte disorders | 1,507 (31%) | 82 (34%) | 0.40 | 10,304 (28%) | 164 (28%) | >0.9 |
| HIV and AIDS | 105 (2.2%) | 7 (2.9%) | 0.50 | 230 (0.6%) | 4 (0.7%) | 0.80 |
| Hypertension, complicated | 94 (2.0%) | 5 (2.1%) | 0.80 | 600 (1.6%) | 9 (1.5%) | 0.80 |
| Hypertension, uncomplicated | 1,325 (28%) | 73 (30%) | 0.40 | 15,014 (41%) | 241 (41%) | >0.9 |
| Hypothyroidism | 219 (4.6%) | 11 (4.6%) | >0.9 | 3,079 (8.5%) | 39 (6.7%) | 0.13 |
| Liver disease | 390 (8.1%) | 34 (14%) | 0.001 | 954 (2.6%) | 16 (2.7%) | 0.90 |
| Lymphoma | 27 (0.6%) | 4 (1.7%) | 0.06 | 486 (1.3%) | 11 (1.9%) | 0.30 |
| Metastatic cancer | 51 (1.1%) | 1 (0.4%) | 0.50 | 772 (2.1%) | 9 (1.5%) | 0.30 |
| Obesity | 515 (11%) | 30 (12%) | 0.40 | 4,871 (13%) | 118 (20%) | <0.001 |
| Other neurological disorders | 765 (16%) | 47 (20%) | 0.14 | 5,084 (14%) | 66 (11%) | 0.07 |
| Paralysis | 146 (3.0%) | 6 (2.5%) | 0.60 | 1,132 (3.1%) | 25 (4.3%) | 0.11 |
| Peripheral vascular disease | 361 (7.5%) | 24 (10.0%) | 0.20 | 3,446 (9.5%) | 68 (12%) | 0.07 |
| Psychoses | 734 (15%) | 50 (21%) | 0.02 | 1,521 (4.2%) | 36 (6.2%) | 0.02 |
| Pulmonary circulation disorders | 322 (6.7%) | 20 (8.3%) | 0.30 | 1,137 (3.1%) | 22 (3.8%) | 0.40 |
| Renal failure | 225 (4.7%) | 15 (6.2%) | 0.30 | 3,182 (8.7%) | 43 (7.4%) | 0.20 |
| Rheumatoid arthritis/collagen vascular diseases | 197 (4.1%) | 13 (5.4%) | 0.30 | 1,352 (3.7%) | 14 (2.4%) | 0.09 |
| **Solid tumor without metastasis** | 170 (3.5%) | 4 (1.7%) | 0.12 | 2,959 (8.1%) | 35 (6.0%) | 0.06 |
| **Valvular disease** | 337 (7.0%) | 26 (11%) | 0.03 | 1,724 (4.7%) | 28 (4.8%) | >0.9 |
| **Weight loss** | 381 (7.9%) | 22 (9.1%) | 0.50 | 2,162 (5.9%) | 43 (7.4%) | 0.15 |
| **Substance use and/or disorder** |  |  |  |  |  |  |
| History of opioid use or disorder | 3,431 (71%) | 177 (73%) | 0.50 |  |  |  |
| History of cocaine use or disorder | 492 (10%) | 30 (12%) | 0.30 |  |  |  |
| History of methamphetamine use or disorder | 1,254 (26%) | 87 (36%) | <0.001 |  |  |  |
| **Injection drug use** | 857 (18%) | 29 (12%) | 0.02 |  |  |  |
| **MOUD** |  |  | 0.80 |  |  |  |
| No MOUD | 2,821 (59%) | 146 (61%) |  |  |  |  |
| Methadone | 1,129 (23%) | 56 (23%) |  |  |  |  |
| Buprenorphine | 856 (18%) | 39 (16%) |  |  |  |  |
| **Infectious diseases diagnosis** |  |  |  |  |  |  |
| Blood stream infection, isolated | 1,844 (38%) | 59 (24%) | <0.001 | 17,782 (49%) | 151 (26%) | <0.001 |
| Osteomyelitis | 1,533 (32%) | 111 (46%) | <0.001 | 12,382 (34%) | 343 (59%) | <0.001 |
| Septic arthritis | 774 (16%) | 54 (22%) | 0.010 | 5,113 (14%) | 103 (18%) | 0.01 |
| Endocarditis | 907 (19%) | 34 (14%) | 0.06 | 2,087 (5.7%) | 19 (3.3%) | 0.01 |
| **Bed size** |  |  | <0.001 |  |  | <0.001 |
| <500 | 746 (16%) | 44 (18%) |  | 6,372 (17%) | 109 (19%) |  |
| 500-999 | 1,659 (35%) | 115 (48%) |  | 12,595 (35%) | 315 (54%) |  |
| >=1000 | 2,398 (50%) | 82 (34%) |  | 17,408 (48%) | 160 (27%) |  |
| Unknown | 3 (<0.1%) | 0 (0%) |  | 61 (0.2%) | 0 (0%) |  |
| **One digit zip code** |  |  | <0.001 |  |  | <0.001 |
| 0 - Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, Puerto Rico, Rhode Island | 543 (11%) | 51 (21%) |  | 3,248 (8.9%) | 41 (7.0%) |  |
| 1 - Delaware, New York, Pennsylvania | 621 (13%) | 15 (6.2%) |  | 4,162 (11%) | 27 (4.6%) |  |
| 2 - District of Columbia, Maryland, North Carolina, South Carolina, Virginia, West Virginia | 514 (11%) | 7 (2.9%) |  | 2,951 (8.1%) | 5 (0.9%) |  |
| 3 - Alabama, Florida, Georgia, Mississippi, Tennessee | 520 (11%) | 19 (7.9%) |  | 4,643 (13%) | 53 (9.1%) |  |
| 4 - Indiana, Kentucky, Michigan, Ohio | 291 (6.1%) | 16 (6.6%) |  | 2,409 (6.6%) | 40 (6.8%) |  |
| 5 - Iowa, Minnesota, Montana, North Dakota, South Dakota, Wisconsin | 105 (2.2%) | 18 (7.5%) |  | 1,300 (3.6%) | 58 (9.9%) |  |
| 6 - Illinois, Kansas, Missouri, Nebraska | 378 (7.9%) | 33 (14%) |  | 3,080 (8.5%) | 159 (27%) |  |
| 7 - Arkansas, Louisiana, Oklahoma, Texas | 197 (4.1%) | 17 (7.1%) |  | 2,385 (6.6%) | 49 (8.4%) |  |
| 8 - Arizona, Colorado, Idaho, New Mexico, Nevada, Utah, Wyoming | 984 (20%) | 30 (12%) |  | 7,658 (21%) | 60 (10%) |  |
| 9 - Alaska, California, Hawaii, Oregon, Washington | 650 (14%) | 35 (15%) |  | 4,569 (13%) | 92 (16%) |  |
| Unknown | 3 | 0 |  | 31 | 0 |  |
| Abbreviations: laLGP, long-acting glycopeptide; MOUD, medication for opioid use disorder;  PWUD, person who uses drugs; non-PWUD, person who does not use drugs; SOC, standard of care antibiotics.  Values in table are n (%) unless otherwise noted.  1 We grouped individuals of American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or mixed racial group as Other race.  2 Fisher’s exact test or two sided t-tests were used to calculate p values. | | | | | | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | PWUD | | | | Non-PWUD | | | |
|  | Overall N = 5,047  n (%) | SOC  N = 4,806  n (%) | laLGP  N = 241  n (%) | p-value1 | Overall N = 37,020  n (%) | SOC  N = 36,436  n (%) | laLGP  N = 584  n (%) | p-value1 |
| **Readmission, 90 days** | 1,954 (39%) | 1,892 (39%) | 62 (26%) | <0.001 | 11,476 (31%) | 11,360 (31%) | 116 (20%) | <0.001 |
| **ER visit, 90 days** | 1,352 (27%) | 1,287 (27%) | 65 (27%) | >0.99 | 6,837 (18%) | 6,740 (18%) | 97 (17%) | 0.20 |
| **Death or hospice, 90 days** | 5 (<0.1%) | 5 (0.1%) | 0 (0%) | >0.99 | 39 (0.1%) | 38 (0.1%) | 1 (0.2%) | 0.50 |
| **Composite: Readmission, ER visit, or death/hospice, 90 days** | 2,599 (51%) | 2,492 (52%) | 107 (44%) | 0.02 | 15,297 (41%) | 15,112 (41%) | 185 (32%) | <0.001 |
| **Abbreviations: laLGP, long-acting glycopeptide; ER, emergency room; PWUD, person who uses drugs; non-PWUD, person who does not use drugs; SOC, standard of care antibiotics.**  **1 Fisher’s exact test was used to calculate p values.** | | | | | | | | |

**Table 2. Unadjusted 90-day outcomes by long-acting glycopeptide use in people who use and do not use drugs admitted due to a serious bacterial infection.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  | |  |
| **Outcome** | Hazard ratio | 95% CI | RMST, difference % | 95% CI |
| **PWUD** | | | | |
| Entire cohort | 1.01 | 0.88 to 1.13 | -0.73 | -4.17 to 2.68 |
| BSI, isolated | 1.06 | 0.83 to 1.32 | -2.04 | -9.01 to 5.12 |
| Osteomyelitis | 1.07 | 0.88 to 1.25 | -2.82 | -8.12 to 2.57 |
| Septic arthritis | 0.88 | 0.71 to 1.07 | 4.22 | -1.81 to 9.96 |
| Endocarditis | 1.09 | 0.84 to 1.35 | -3.67 | -12.59 to 5.28 |
| laLGP vs. Vancomycin | 0.90 | 0.77 to 1.03 | 2.24 | -1.56 to 6.14 |
| laLGP vs Cefazolin | 0.97 | 0.81 to 1.13 | 0.66 | -3.05 to 4.66 |
| **Non-PWUD** | | | | |
| Entire cohort | 0.93 | 0.86 to 1.00 | 1.76 | 0.03 to 3.91 |
| BSI, isolated | 0.99 | 0.98 to 1.13 | 0.55 | -3.36 to 4.23 |
| Osteomyelitis | 0.85 | 0.76 to 0.96 | 3.28 | 0.71 to 5.57 |
| Septic arthritis | 0.93 | 0.76 to 1.10 | -0.12 | -3.26 to 5.35 |
| Endocarditis | 1.01 | 0.96 to 1.13 | -4.03 | -20.86 to 10.6 |
| laLGP vs. Vancomycin | 0.84 | 0.76 to 0.92 | 3.98 | 1.78 to 6.00 |
| laLGP vs Cefazolin | 0.87 | 0.79 to 0.96 | 3.02 | 0.76 to 5.14 |
| **Abbreviations:**  **BSI, bloodstream infection;** **laLGP, long-acting glycopeptide; RMST, restricted mean survival time; PWUD, person who uses drugs; non-PWUD, person who does not use drugs.**  **Hazard ratios of less than 1 favor laLGPs and hazard ratios of more than 1 favor the comparator group (grouped standard of care antibiotics or vancomycin or cefazolin, where noted).**  **RMST difference of more than 0 favor laLGPs and RMST difference of less than 0 favor the comparator.** | | | | |

**Table 3. Hazard ratios, restricted mean survival time, and 95% confidence intervals of 90-day outcomes in analysis of people who use and do not use drugs admitted due to a serious bacterial infection and received a long-acting glycopeptide compared to those who did not.**

**Figure 1. Consort diagram.**

**Figure 2. Temporal trends and geographic distribution of laLGP use for serious bacterial infections in the United States (October 2015 – October 2022).** Panel A shows trends in laLGP use by specific drug. Panel B shows trends in laLGP use over time by infectious disease diagnosis. Panel C shows the percentage of serious bacterial infections treated with laLGP in different geographic regions.