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Automated Alerts to Improve Timely Evaluation and Treatment of Valvular Heart Disease: The ALERT Trial

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ABSTRACT

Background: Severe aortic stenosis (AS) and mitral regurgitation (MR) are frequently undertreated and characterized by persistent sex, racial and ethnic, socioeconomic, and geographic disparities despite effective valve therapies. Whether automated electronic clinician notification (ECN) alerts improve the evaluation and treatment of AS and MR across health systems is unknown.

Objective: To evaluate whether ECN alerts improve guideline-directed evaluation and treatment of significant AS and MR across multiple health systems.

Methods: ALERT is a multisystem, cluster-randomized clinical trial including clinicians ordering echocardiograms across 5 US health systems encompassing 35 hospitals between August 2024 and September 2025. Clinicians were randomized 1:1 to receive an ECN alert identifying significant AS or MR with accompanying care recommendations, or to no alert with usual care. The primary endpoint was a hierarchical composite of time to surgical or transcatheter valve intervention, followed by time to multidisciplinary heart team (MHT) clinic evaluation within 90 days, analyzed using the stratified win ratio method. Secondary outcomes included individual components of the composite.

Results: A total of 765 clinicians ordering 2,016 echocardiograms were included. In the win ratio analysis of the primary endpoint, ECN alert was superior to usual care (win ratio, 1.27; 95% CI, 1.05–1.54; $P = .007$), including higher rates of valve intervention (12.9% vs 9.3%; $P = .013$) and MHT evaluation (22.2% vs 17.6%; $P = .014$) and shorter times to both endpoint components. Effect sizes were similar in AS (win ratio, 1.29) and MR patients (win ratio, 1.23). No evidence of heterogeneity was noted by valve

pathology (P_{int} = .82) or across prespecified subgroups (age, sex, race, social deprivation index, inpatient vs. outpatient setting, provider specialty, and rurality; P_{int} > .10 for all) and sensitivity analyses yielded consistent results across modified intention-to-treat, intention-to-treat, and per-protocol populations.

Conclusions: In this multisystem cluster randomized trial, automated ECN alerts improved timely guideline-directed evaluation and valve intervention for clinically significant AS and MR. These findings suggest that EHR-integrated clinical decision support may represent a scalable strategy to reduce undertreatment and improve access to specialized valve care.

CONDENSED ABSTRACT

ALERT assessed whether ECNs improve evaluation and treatment of AS and MR and included 765 clinicians that ordered 2,016 echocardiograms across 5 US health systems. Primary endpoint analysis through 90 days indicated ECN alert was superior to usual care (win ratio, 1.27; 95% CI, 1.05–1.54; P=.007), with higher rates of valve intervention (12.9% vs 9.3%; P=.013) and MHT evaluation (22.2% vs 17.6%; P=.014). There was no evidence of heterogeneity by valve pathology (P_{int}=.82) or across demographic subgroups (P_{int}>.10 for all). Results suggest that ECNs may help reduce undertreatment of VHD and improve access to specialized valve care.

Keywords: Aortic stenosis; Mitral regurgitation; Automated notifications; Electronic health record; Clinician decision support; Health equity

Abbreviations: ALERT: Addressing undertreatment and heaLth Equity in aortic stenosis and mitral regurgitation using an integrated ehR plaTform; AS: Aortic stenosis; AVR: Aortic valve replacement; CDS: Clinical decision support; EHR: Electronic health record; ECN: Electronic clinician notification; MHT: Multidisciplinary heart team; MR: Mitral regurgitation; TAVR: Transcatheter aortic valve replacement; VHD: Valvular heart disease.

INTRODUCTION

Aortic stenosis (AS) and mitral regurgitation (MR) are the most common forms of valvular heart disease (VHD) requiring intervention in developed countries, with prevalence increasing as the population ages. Severe AS affects more than 3% of adults older than 75 years, while moderate-to-severe or severe MR affects approximately 2% to 3% of adults aged 65 years or older. [1-3] In the absence of surgical or transcatheter valve intervention, both conditions are associated with impaired quality of life, increased morbidity, and reduced survival. Mortality among patients with untreated severe symptomatic AS approaches 50% within 2 years,[4,5] and certain hemodynamic subsets of asymptomatic patients are also at high risk of adverse outcomes.[6,7] Conservatively managed severe MR, even when asymptomatic, is similarly associated with progressive heart failure and premature death.[8,9] Accordingly, contemporary American and European VHD guidelines and clinical performance measures emphasize multidisciplinary heart team (MHT) evaluation and timely surgical or transcatheter valve intervention, including a 90-day performance benchmark for intervention in patients with severe AS and chronic severe MR.[10-12]

Despite major advances in valve therapies, substantial growth in aortic and mitral valve procedure volumes, and improved procedural outcomes,[13,14] undertreatment and delays in care remain common. Fewer than half of patients with severe AS who meet ACC/AHA Class I or IIa recommendations for aortic valve replacement undergo intervention,[15,16] and similar treatment gaps exist for severe MR.[8,9] The likelihood of receiving valve intervention varies substantially by treating physician, with marked

heterogeneity even among cardiologists, and patients managed by clinicians with lower rates of valve intervention experience higher risk-adjusted mortality.[15,17] Access to valve intervention is also uneven, with women, racial and ethnic minority populations, older adults, patients with greater social deprivation, and rural residents less likely to receive intervention even after adjustment for comorbidities and disease severity.[2,18-22] These disparities reflect a complex interplay of patient-, clinician-, and system-level factors. [23]

Automated electronic clinician notification (ECN) alerts have been proposed as a scalable strategy to improve recognition and treatment of severe VHD. The Electronic Provider Notification to Facilitate the Recognition and Management of Severe Aortic Stenosis (DETECT-AS) trial demonstrated that ECN alerts were associated with higher rates of aortic valve replacement (AVR) among patients with severe symptomatic AS.[24] However, DETECT-AS was conducted within a single integrated health system with limited racial diversity (96% White) and focused exclusively on AS. The Addressing undertreatment and heaLth Equity in aortic stenosis and mitral regurgitation using an integrated ehR plaTform (ALERT) trial[25] was designed to address these limitations. ALERT evaluated whether fully automated, EHR-integrated ECN alerts generated through natural language processing (NLP) of echocardiography reports improve adherence to guideline-based performance metrics, including timely MHT clinic evaluation and valve intervention, among patients with significant AS or MR across 5 US health systems encompassing 35 hospitals. The trial was designed to determine whether this scalable digital strategy could improve delivery of guideline-directed care and reduce undertreatment across diverse patient populations and care settings.

METHODS

Trial Design and Oversight:

The ALERT trial was a multicenter, cluster-randomized clinical trial conducted across 5 US health systems and designed as a superiority trial (Supplemental Appendix). The study rationale and design have been published previously,[25] and the full protocol and statistical analysis plan are provided in Supplemental Material. Due to the complexity and proprietary nature of the dataset, and the potential risks to participant privacy, the data are not currently available for public distribution. The protocol was approved by a central institutional review board (Advarra IRB Pro00071710) with a waiver of informed consent for patients and clinicians. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was registered at ClinicalTrials.gov (NCT06099665).[26]

Study Population:

Enrollment occurred between August 2024 and September 2025 across 5 US health systems encompassing 35 hospitals and 90-day follow-up was completed for all patients. Eligible patients were adults (≥18 years) with echocardiographic evidence of significant AS or MR. Significant AS was defined as definite or potentially severe AS based on the presence of any of the following criteria: aortic valve area ≤1.0 cm^2, dimensionless index ≤0.25, mean aortic valve gradient ≥40 mm Hg, peak aortic valve gradient ≥64 mm Hg, or peak aortic valve jet velocity ≥4.0 m/s. Significant MR was defined as moderate-to-severe or severe MR based on the qualitative classification of

severity in the echocardiography report. While quantitative measures of MR severity may have also been included in echocardiogram reports, the qualitative classification of severity was prioritized for inclusion in the study for consistency, since quantitative measures are not consistently reported across studies.[27] Eligible echocardiograms were those ordered by clinicians who were not members of the MHT. The MHT members were identified by each site and included interventional and imaging cardiologists as well as all cardiac surgeons. Patients were excluded for prior surgical or transcatheter valve intervention, prosthetic VHD, scheduled MHT visit or planned valve intervention, or evaluation by a MHT member.

The intention-to-treat population included all patients associated with randomized clinicians. The modified intention-to-treat population excluded patients for whom an ECN alert could not be delivered because of site-level technical restrictions or lack of clinician access to the electronic health record (EHR). The per-protocol population further excluded patients in the modified intention-to-treat population whose clinicians should have but did not receive an ECN alert; patients in the control group who erroneously received an ECN alert (contamination); and patients enrolled despite not meeting eligibility criteria. The modified intention-to-treat population was prespecified as the primary analytic population, with intention-to-treat and per-protocol population analyses planned as sensitivity analyses.

Randomization and Intervention:

Randomization was performed at the clinician level in a 1:1 ratio, stratified by site and historical echocardiogram volume. Clinicians were randomized to either the ECN Alert (treatment) or No-Alert (control) group and remained in their assigned group and blinded to treatment allocation for the duration of the trial. The randomization allocation sequence was programmed and validated by Tempus software engineers prior to study initiation and fully automated in the Tempus Next platform throughout the study. Clinicians in the ECN Alert group received notifications for all patients meeting inclusion criteria. All electronic alerts were delivered to the clinician's EHR inbox; patients were not notified of the alert. To reduce imbalance, randomization was stratified by the number of echocardiograms ordered in a two-month pre-enrollment quality control period at each site, with three strata: ≤1, 2–10, or >10 echocardiograms. Clinicians without retrospective data were randomized upon receiving their first qualifying patient. This approach ensures comparable group sizes and minimized potential contamination by provider experience. All randomization assignments were systematically recorded in the Tempus database, which included consent status, randomization status, and group assignment for every clinician. To maintain blinding, all site personnel, including principal investigators, data analysts, and biostatisticians, were restricted from accessing allocation information or sequencing codes within Tempus Next. Allocations were only accessible by designated Tempus personnel, and every assignment was tracked through an immutable audit log within the study platform.

Automated Electronic Notification Alert Platform and Logic:

The Tempus Next platform utilized NLP to extract structured and unstructured data from echocardiogram reports, with a previously validated detection accuracy of 98.6% for severe AS.[28] Echocardiogram values measured, but not reported, were not detected by the NLP model. Clinicians assigned to the ECN Alert group received notifications according to the setting in which the echocardiogram was performed (inpatient vs. outpatient). For inpatient echocardiograms, ECNs were delivered 5 days after hospital discharge using the following prespecified hierarchical routing algorithm to generate a single alert: first to the cardiologist who ordered the echocardiogram or provided the most recent care during the enrollment period; next to the most recent primary care clinician identified in structured echocardiography report fields or by recent clinical documentation; and last to the non-cardiologist clinician who ordered the echocardiogram. ECN alerts were sent only if no valve intervention or MHT team member evaluation occurred during the index hospitalization. For outpatient echocardiograms, ECNs were delivered to the ordering clinician 1 to 5 days after the index study. All inpatient and outpatient ECN alerts were accompanied by site specific guideline-based care recommendations (Supplemental Appendix, Site Specific Alert Messages).

Primary and Secondary End points:

The primary end point was a hierarchical composite assessed using a stratified win-ratio method, prioritizing time to surgical or transcatheter valve intervention followed by time to MHT clinic visit within 90 days after the index echocardiogram. Secondary end points included the individual components of the primary endpoint. There was a prespecified plan to evaluate outcomes within each valve pathology (AS and MR) and prespecified subgroup analyses were performed according to age, sex, race and ethnicity, hospital site, provider specialty, inpatient vs. outpatient setting, social deprivation index (SDI) and rurality.

Statistical Analysis:

We estimated a sample of 1,246 patients would provide the trial with >80% power to show the superiority of ECNs to usual care at a one-sided alpha of 2.5% with regard to the primary endpoint at 90-days, assuming a 5% absolute increase in the separate components of the hierarchical endpoint, varying correlations between the endpoint components and intracluster correlation within referring physicians.

The primary end point was analyzed using a stratified (AS or MR) win-ratio approach, as previously described,[29] with comparisons prioritized by time to surgical or transcatheter valve intervention and, if tied, by time to MHT clinic visit within 90 days after the index echocardiogram. Patients were right censored at the time of a subsequent qualifying echocardiogram within 90 days or at death during the follow-up period. The win ratio statistics are reported with a two-sided 95% confidence interval and one-sided *P*-value evaluating superiority. A one-sided *P*-value < .025 was considered statistically

significant. Subgroup analyses and interaction P-values were calculated using the methods of Pocock et al.[30] To aid interpretation of the primary endpoint, the net benefit was also reported, with a two-sided 95% CI.[31] A cumulative incidence function (CIF) analysis was performed for the composite care delivery endpoint of time to valve intervention or MHT clinic visit, with death treated as a competing risk[32]. Differences between treatment arms were assessed using a two-sided Gray's test.[32]

Secondary endpoint analyses evaluated the association between ECN alerts and time to event (MHT clinic visit, valve intervention, and the composite endpoint of first event) using multivariable Cox proportional hazards regression models. Models were constructed for the overall cohort and separately for the AS and MR groups, adjusting for age >80 years, sex, race (black vs. non-black), high SDI (>median), inpatient status, site (as a fixed effect), specialty (cardiologist vs. non-cardiologist), location (rural vs urban), and LVEF ≤40%. Kaplan–Meier (KM) methods were used to estimate time-to-event distributions for MHT clinical visit and valve intervention through 90 days, with between-group differences assessed using the log-rank test. For the composite endpoint (time to first MHT clinic visit or valve intervention), the risk difference was calculated as the difference between KM event rates, with 95% confidence intervals derived using Greenwood standard errors. Restricted mean survival time (RMST) was also estimated with corresponding 95% confidence intervals.[33]

To evaluate transitions across stages of care and assess subgroup effects, a prespecified multistate model was fitted with 3 states: (1) index echocardiogram demonstrating potentially significant AS or MR; (2) MHT evaluation; and (3) valve

intervention. Win ratio analyses comparing ECN to usual care were performed for the following AS subgroups: AS with high (mean gradient ≥40 mm) vs. low (mean gradient < 40 mm Hg) valve gradients; and for the following MR subgroups: moderately-severe MR, severe MR, MR with left ventricular ejection fraction (LVEF) ≥ 50%, and MR with LVEF < 50%. Unless stated otherwise, all *P*-values reported are one-sided. All statistical analyses were performed using R version 4.4.1 statistical software (R Foundation for Statistical Computing, Vienna, Austria) using the BuyseTest R package version 3.3.4.[31]

RESULTS

Study Population

The CONSORT flow diagram is shown in Figure 1. Among 147,122 echocardiograms ordered by 6,523 clinicians across 35 hospitals in 5 U.S. health systems, 783 clinicians ordering 2,118 echocardiograms met eligibility criteria and comprised the intention-to-treat population. Clinicians were randomized to receive an ECN alert (Alert: 394 clinicians; 1,239 echocardiograms) or to usual care (No-Alert: 389 clinicians; 879 echocardiograms). Eighteen clinicians (102 echocardiograms) were excluded from the intention-to-treat population due to site-level technical limitations that prevented the delivery of ECNs. The resulting modified intention-to-treat population included 765 clinicians, and 2,016 echocardiograms performed in 1905 patients. Of these, 376 clinicians (1,137 echocardiograms) were allocated to the Alert group, and 389 clinicians (879 echocardiograms) to usual care (No-Alert group). This population constituted the primary analysis cohort. During 90-day follow-up, 61/1905 deaths occurred (3.2%),

including 43/1054 (4.1%) in the Alert group and 18/851 (2.1%) in the No Alert group. Deaths were right censored, per the prespecified protocol. The per-protocol population consisted of 710 clinicians and 1,653 echocardiograms, following exclusion of 363 echocardiograms from the modified intention-to-treat population due to protocol deviations. Within the per-protocol population, 332 clinicians (861 echocardiograms) were assigned to the Alert group and 378 clinicians (792 echocardiograms) to usual care (No-Alert group).

Baseline Characteristics

Baseline patient characteristics were generally similar between groups (Table 1). The ECN group included a higher proportion of women (54% vs 49%) and non-Hispanic patients (70% vs 64%) compared with usual care. The distribution of AS and MR did not differ between groups; however, qualifying echocardiograms were more frequently obtained in the inpatient setting in the ECN group than in the usual care group (42% vs 33%). Baseline characteristics of the intention-to-treat (Supplemental Table 1) and per-protocol populations (Supplemental Table 2), and patient disposition (Supplemental Table 3), were also similar between groups.

Primary and secondary endpoints

Primary Endpoint. Compared with usual care, ECN was superior for the primary hierarchical composite end point (overall stratified win ratio, 1.27; 95% CI, 1.05–1.54; *P* = .007) (Figure 2). The corresponding net benefit was calculated as 4.21% (95% CI:

0.63% to 7.77%). Sensitivity analyses demonstrated that ECN was superior for the primary hierarchical composite end point within the intention-to-treat (stratified win ratio, 1.24; 95% CI, 1.02–1.49; $P < .001$) and per-protocol populations (stratified win ratio, 1.50; 95% CI, 1.22–1.85; $P < .001$); Supplemental Figures 1 and 2. Prespecified subgroup analyses showed no evidence of heterogeneity of treatment effect across age, sex, race, social deprivation, inpatient vs. outpatient setting, health system, provider specialty, or rural vs. urban setting (Figure 3). The cumulative incidence function (CIF) analysis for the composite care delivery endpoint of time to valve intervention or MHT clinic visit, treating death as a competing risk, demonstrated that the Alert arm was associated with higher probability of receiving care within 90 days compared with the No Alert arm (24% vs. 20%; p=0.027).

Secondary endpoints. Kaplan–Meier (KM) analyses showed that ECN alerts were associated with shorter time to the primary composite endpoint (MHT visit or valve intervention; Figure 4). Findings were similar in the intention-to-treat and per-protocol populations (Supplemental Figures 3 and 4). For the composite endpoint, KM event rates at 90-days were 24.3% and 19.9% in the ECN alert and usual care groups, respectively. Time to first MHT visit or valve intervention (RMST) was 2.5 days (95% CI: 0.1-4.9) shorter in the ECN arm. In a supportive multistate model of the modified intention-to-treat population (Supplemental Table 4), ECN alerts were associated with a nonsignificant trend toward faster transitions from echocardiogram to MHT visit (HR, 1.21; 95% CI, 0.99–1.48; $P = .034$) and from MHT visit to valve intervention (HR, 1.37;

95% CI, 1.00–1.89; *P* = .026), and no faster transition from echocardiogram directly to valve intervention (HR, 0.94; 95% CI, 0.50–1.77; *P* = .57). Multivariable predictors of the composite endpoint (MHT visit or valve intervention) are presented in Supplemental Table 5 for the overall cohort, and in Supplemental Table 6 for the AS and MR groups analyzed separately. In the overall cohort, receipt of an ECN alert and care at site C (referenced to site D) were associated with an increased hazard of the composite endpoint. In contrast, age > 80 years, female sex, black race, inpatient status, and site B were associated with a reduced hazard. Within the AS group, ECN alert, site C, and mean aortic valve gradient ≥ 40 mmhg were associated with an increased hazard of the composite endpoint, whereas age > 80 years, female sex, and site B were associated with a reduced hazard. Within the MR group, age > 80 years, inpatient status, and care at site B were associated with a reduced hazard of the composite endpoint.

Results in Aortic Stenosis Subgroup

Win ratio analysis of the primary endpoint in AS (Figure 2) showed ECN alerts were superior to usual care (win ratio, 1.29; 95% CI, 1.01–1.65; *P* = .019). Sensitivity analyses showed win ratios 1.26 (95% CI, 0.99–1.60; *P* = .03) in the intention-to-treat population (Supplemental Figure 1) and 1.54 (95% CI, 1.18–2.00; *P* < .001) in the per-protocol population (Supplemental Figure 2). Kaplan–Meier analyses showed a nonsignificant trend favoring ECN alerts for time to MHT visit (cumulative probability at 90 days: 23.0% vs 19.3%; log-rank *P* = .07) and a significant difference in favor of ECN alerts for time to valve intervention (cumulative probability at 90 days: 14.8% vs 9.2%;

log-rank *P* = .002) (Supplemental Figure 5). Similar findings were observed in the AS intention-to-treat population and per-protocol populations (Supplemental Figures 6 and 7), with larger between-group differences noted in the latter population. In a multistate model of the modified intention-to-treat AS population (Supplemental Table 4), ECN alerts were associated with a faster transition from MHT visit to valve intervention (HR 1.49; 95% CI, 1.01-2.18; *P*=0.021), a nonsignificant trend toward faster transition from echo directly to valve intervention (HR, 2.47; 95% CI, 0.80–7.66; *P* = .059), and no difference in transition time from echocardiogram to MHT visit (HR, 1.12; 95% CI, .87–1.44; *P* = .192). Post hoc analysis of the AS subgroup showed the win ratio for ECN vs. usual care was 1.67 (95% CI, 1.16–2.42; *P* = .003) in patients with high-gradient AS (mean gradient ≥40 mm Hg) and 1.15 (95% CI, 0.83–1.60; *P* = .20) in patients with low-gradient AS (mean gradient <40 mm Hg) (Supplemental Table 7).

Results in Mitral Regurgitation Subgroup

Among patients with MR, win ratio analysis of the primary endpoint comparing ECN alerts to usual care was 1.23 (95% CI, 0.90–1.69; *P* = 0.094) (Figure 2). Sensitivity analyses in the intention-to-treat and per protocol populations showed win ratios of 1.20 (95% CI, 0.88–1.64; *P* = .12) and 1.45 (95% CI, 1.03–2.04; *P* = .017), respectively (Supplemental Figures 1 and 2). Kaplan–Meier analyses demonstrated earlier MHT team evaluation in the ECN alert group (cumulative probability at 90 days: 22.2% vs 15.6%; log-rank *P* = .009), but no difference in time to valve intervention (cumulative probability at 90 days: 11.3% vs 10.1%; log-rank *P* = .32) (Supplemental Figure 8). Similar findings

were observed in the intention-to-treat (Supplemental Figure 9) and per-protocol populations (Supplemental Figure 10). In a multistate model of the modified intention-to-treat MR population (Supplemental Table 4), ECN alerts were associated with a nonsignificant trend toward faster transitions from echocardiography to MHT visit (HR1.40; 95% CI, 0.99-1.98; *P* = .030) and no difference in transition time from echocardiogram to valve intervention (HR 0.51; 95% CI, 0.22–1.18; *P* = .941) or from MHT visit to valve intervention (HR, 1.16; 95% CI, 0.64–2.10; *P* = .310). Post hoc win ratio analyses within MR subgroups according to MR severity and LVEF are shown in (Supplemental Table 7).

DISCUSSION

In this large, multicenter, cluster-randomized trial, automated ECN alerts improved the timely evaluation and treatment of clinically significant AS and MR across 35 hospitals in 5 U.S. health systems. Using a stratified win-ratio analysis of the hierarchical composite endpoint of valve intervention or MHT clinic visit, ECN alerts resulted in higher rates of both MHT clinic visits and valve intervention and shorter times to evaluation and treatment. These benefits were consistent across prespecified patient, provider, and care-setting subgroups, independent of competing risks of death, and robust across sensitivity analyses in the intention-to-treat, modified intention-to-treat, and per-protocol populations. Collectively, these findings demonstrate that EHR-integrated

clinical decision support can improve the delivery of guideline-directed care for VHD by transforming existing diagnostic information into clinical action.

Timely identification and treatment are central to improving outcomes in severe VHD, where delayed or absent intervention is associated with substantial morbidity and mortality.[4,5,7,9,11,12] Consistent with this principle, the 2024 ACC/AHA Clinical Performance and Quality Measures Report identifies valve intervention within 90 days for adults with severe symptomatic AS or chronic severe MR as a key performance metric.[10] The ALERT trial's 90-day primary endpoint was intentionally aligned with these standards. Although the overall treatment effect of ECN alerts was consistent across analytic populations and directionally similar for AS and MR, variability in effectiveness was observed across sites. This likely reflects differences in institutional readiness, technical integration, and workflow alignment—factors commonly encountered when scaling digital health interventions across health systems. ECN alerts improved care delivery despite these implementation challenges, supporting the robustness and generalizability of the findings. These observations highlight that successful deployment of AI-enabled clinical decision support requires alignment of technology, clinical workflow, and institutional infrastructure, underscoring the importance of implementation strategy alongside algorithm development.

Differences were also observed in the downstream care pathways according to valve pathology. Among patients with AS, the higher rate of valve intervention associated with ECN alerts appeared to be driven by faster progression from the index

echocardiogram directly to valve intervention, likely reflecting surgical AVR, as well as a shorter interval from MHT clinic to valve intervention, with no difference in time to transition from index echocardiogram to MHT clinic visit (Supplemental Table 4). In contrast, among patients with MR, ECN alerts were associated with a trend toward faster transition from index echocardiogram to MHT evaluation but had no measurable impact on progression to valve intervention within the study's 90-day follow-up timeframe. These differences likely reflect fundamental distinctions in the routine clinical evaluation and management of AS and MR. Severe symptomatic AS carries a Class I indication for surgical or transcatheter aortic valve replacement,[11] and once identified, progression to intervention is typically straightforward and less prone to delay. Patients eligible for surgical AVR may proceed directly to surgery without MHT evaluation, and while transcatheter valve candidates require MHT assessment there is usually a straight path to valve intervention. In contrast, severe MR, particularly secondary MR, often requires optimization of guideline-directed medical therapy with serial reassessment of ventricular function before valve intervention is considered.[11] Consequently, a 90-day timeframe may underestimate the full impact of ECN alerts on valve intervention for MR, and longer follow-up necessary to fully capture care pathway acceleration.

Prior studies have demonstrated lower rates of referral and valve intervention for severe VHD among historically underserved populations, including women, Black patients, rural residents, and individuals with greater social deprivation.[2,18-22] In multivariable analysis, ECN alerts in our study were independently associated with MHT clinic visits and valve intervention, with no evidence of heterogeneity in treatment effect

across age, sex, race, social deprivation, care setting, provider specialty, health system, or rurality. However, consistent with prior reports, advanced age (>80 years), female sex, Black race, inpatient status, and one treatment site were associated with lower likelihood of MHT evaluation and valve intervention. These findings suggest that although the relative benefit of ECN alerts was preserved across historically underserved populations, EHR-integrated alerts alone are insufficient to eliminate persistent structural biases and treatment disparities, underscoring the need for sustained system-level interventions to address these gaps.

The findings of ALERT complement those of the DETECT-AS trial,[24] which also demonstrated higher rates of AVR following electronic provider notifications within a single integrated health system. ALERT extends this prior work by demonstrating effectiveness across a larger and more heterogeneous care environment that encompassed 35 hospitals across 5 health systems, a more racially and ethnically diverse patient population, and 2 types of valve pathology (AS and MR). In addition, ALERT evaluated a hierarchical endpoint that prioritized timely MHT evaluation and valve intervention, aligning with contemporary guideline recommendations and quality performance metrics.[10-12] Despite this, referral and treatment rates remain suboptimal. In DETECT-AS, electronic notifications increased AVR rates among symptomatic AS patients from 27.6% to 36.9% at 90 days, and from 47.0% to 60.1% at 1 year.[24] In ALERT, even with ECN alerts, only 45% of patients with severe high-gradient AS and 30% of patients with severe MR were referred for MHT evaluation within 90 days. These findings highlight an opportunity to further improve care delivery.

Many AS and MR patients with Class I indications for valve intervention do not undergo treatment, often without documented contraindications or uncertain symptom attribution.[2,8,16,33,34] Despite clear guideline recommendations, referral rates vary substantially across clinicians and institutions, suggesting the presence of clinical inertia.[11,12,15,35,36] In our study, the likelihood of MHT evaluation and valve intervention varied across sites and valve hemodynamics, with high-gradient (≥40 mmHg) AS patients more likely to undergo evaluation and treatment. These findings indicate that while ECN alerts can meaningfully improve care delivery, additional system-level strategies are required to further reduce heterogeneity and undertreatment. Potential approaches include facilitated referral workflows, "opt-out only" referral mechanisms, direct-to-patient notifications, and longitudinal care pathway monitoring.[37,38] Future studies are needed to evaluate whether integrating EHR-based clinical decision support with these strategies further accelerates care delivery and translates into long term improvements in clinical outcomes.

LIMITATIONS

This study has several limitations. Despite stratified cluster randomization, residual confounding related to site-level practice patterns, referral networks, and institutional resources cannot be excluded. Implementation varied across sites, including differences in alert wording, clinician awareness, and referral-support infrastructure, which may have contributed to heterogeneity in effect. However, this form of variability reflects real-world deployment conditions, enhancing the external validity of results.

Since the effectiveness of ECN alerts depends on clinician engagement, alert fatigue, competing clinical priorities, or clinical inertia may have attenuated the effect size. EHR-integrated clinical decision support also required substantial technical and institutional resources, which limited participation at some sites and may impact generalizability. Deployment-related failures occurred in the ECN arm and were retained in the modified intention-to-treat analysis, representing a conservative analytic approach that would be expected to bias treatment estimates toward the null. The per-protocol analysis reflects the efficacy of ECN alerts when delivered as intended.

Alerts were clinician-directed rather than automated referral pathways. Although this design preserved clinical judgment, automated referral mechanisms may further reduce variability in care delivery and warrant future evaluation. Outcome ascertainment may not have captured care delivered outside participating health systems. The 90-day follow-up period aligned well with contemporary performance benchmarks for timely valve intervention but did not assess longer-term outcomes. Because mortality data were obtained through HL7 interface feeds, it is possible that some events may not have been captured. Finally, digital alerts alone are unlikely to ensure sustained improvement and must be paired with local clinical pathways and institutional readiness to translate alerts into effective clinical action.

CONCLUSIONS

In this multisystem cluster randomized trial, automated ECN alerts improved the timeliness of guideline-directed evaluation and valve intervention for clinically

significant AS and MR across diverse patient populations, care settings, and health systems. These findings suggest that EHR-integrated clinical decision support may represent a scalable strategy to reduce the undertreatment of VHD and improve timely access to specialized care.

LESSONS LEARNED

The ALERT trial demonstrated that, relative to usual care, automated ECN alerts improve guideline-directed evaluation and valve intervention for patients with significant AS and MR, illustrating how scalable digital tools can translate existing diagnostic information into clinical action within health systems. These alerts function as an adjunctive, AI-enabled clinical decision support that may enhance, but not replace, clinician judgment by prompting appropriate care pathways in response to significant findings already documented in the EHR. Variation in effectiveness across sites highlights the importance of alert design, workflow integration, and institutional readiness. Although ECN alerts improved care processes, persistent treatment disparities remain and require continued attention

TABLES

Table 1. Baseline Characteristics

Characteristic	No. (%) based on number of echoes		
	ECN (Alert) Clinicians = 376 Echos =1137	**Usual Care (No Alert) Clinicians = 389 Echos =879**	***P* Value***
Age, mean (± SD), years	76.2 ± 12.8	76.1 ± 12.9	.788
Sex			.048
Male	528 (46%)	448 (51%)	
Female	609 (54%)	431 (49%)	
Race			.596
White	914 (80%)	719 (82%)	
Black	178 (16%)	128 (15%)	
Other	45 (4.0%)	31 (3.5%)	
Unknown	0 (0%)	1 (0.1%)	
Ethnicity			.002
Non-Hispanic	800 (70%)	559 (64%)	
Hispanic	37 (3.3%)	46 (5.2%)	
Unknown	300 (26%)	274 (31%)	
Disease state			.817
Aortic stenosis	705 (62%)	550 (63%)	
Mitral regurgitation	432 (38%)	329 (37%)	
Patient Setting			<.001
Inpatient	477 (42%)	289 (33%)	
Outpatient	640 (56%)	571 (65%)	
Other	20 (1.8%)	19 (2.2%)	

New York Heart Association class			.821
I	19 (1.7%)	14 (1.6%)	
II	51 (4.5%)	30 (3.4%)	
III	71 (6.2%)	75 (8.5%)	
IV	34 (3.0%)	17 (1.9%)	
Unknown	962 (85%)	743 (85%)	
Mitral stenosis	36 (3.2%)	32 (3.6%)	.619
Tricuspid regurgitation	184 (16%)	158 (18%)	.309
Aortic regurgitation	107 (9.4%)	104 (12%)	.091
Moderate MR (in AS Group)	88 (12%)	76 (14%)	.500
Moderate AS (in MR Group)	12 (2.8%)	15 (4.6%)	.235
Comorbidities			
Cerebrovascular disease	292 (26%)	240 (27%)	.415
Coronary artery disease	537 (47%)	413 (47%)	.928
Hypertension	992 (87%)	747 (85%)	.151
Atrial fibrillation	482 (42%)	381 (43%)	.683
Heart failure	683 (60%)	507 (58%)	.294
Diabetes mellitus	374 (33%)	280 (32%)	.632
Echocardiographic data, mean ± SD or N (%)			
AV area, cm^2 (AS only)	0.85 ± 0.21	0.86 ± 0.19	.597
AV mean gradient, mmHg (AS only)	30.6 ± 12.8	30.9 ± 12.2	.661
AV peak gradient, mmHg (AS only)	50.6 ± 20.1	51.0 ± 20.0	.762
AV peak velocity, m/s (AS only)	3.50 ± 0.70	3.52 ± 0.67	.549
Left-ventricular ejection fraction, %	52.0 ± 16.3	53.1 ± 15.7	.121
Mean gradient ≥ 40 mmHg (AS only)	161 (23%)	131 (24%)	.637

Health System			<.001
A	433 (38%)	310 (35%)	
B	359 (32%)	253 (29%)	
C	184 (16%)	214 (24%)	
D	115 (10%)	52 (5.9%)	
E	46 (4.0%)	50 (5.7%)	
Social Deprivation Index, mean ± SD	40.0 ± 28.0	39.3 ± 28.3	.422
Rural vs urban			.851
Urban	840 (74%)	658 (75%)	

*2 sided *P*-value.

Abbreviations: ECN=electronic clinician notification; MR=mitral regurgitation; AS=aortic stenosis; SD: standard deviation; AV = aortic valve

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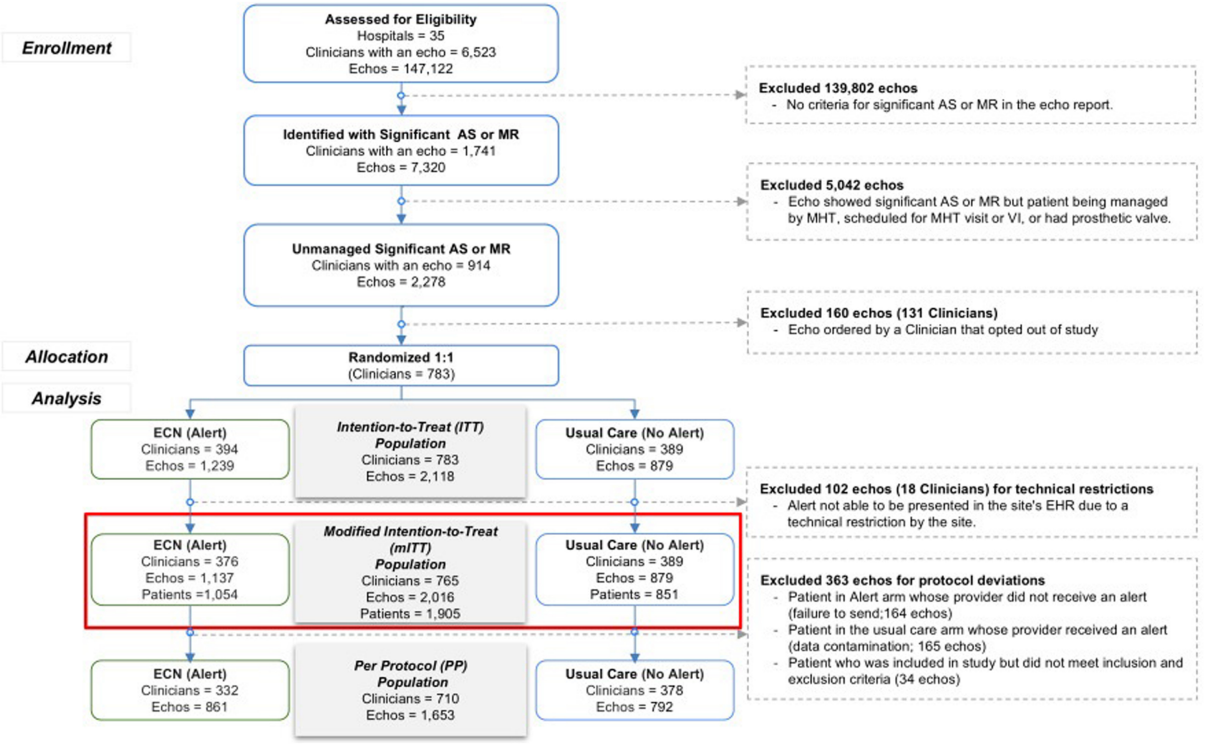
FIGURE LEGENDS

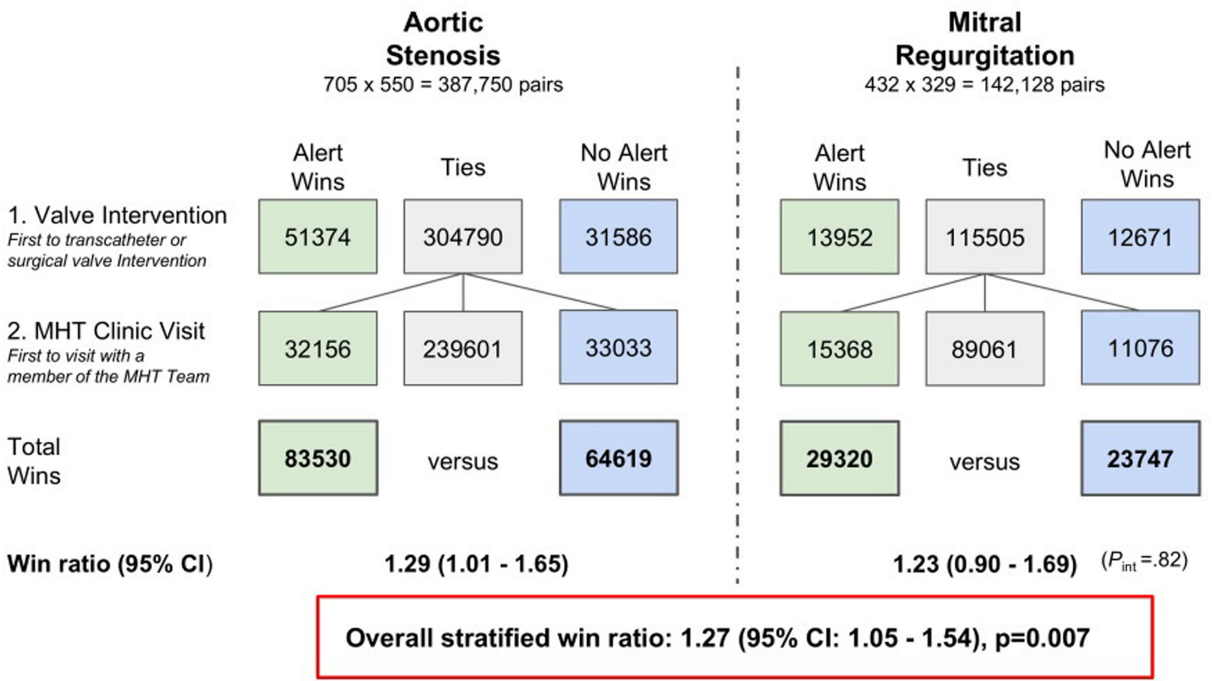
Figure 1. CONSORT Flow Diagram for the ALERT Trial. AS = aortic stenosis; MR = mitral regurgitation; VI = valve intervention.

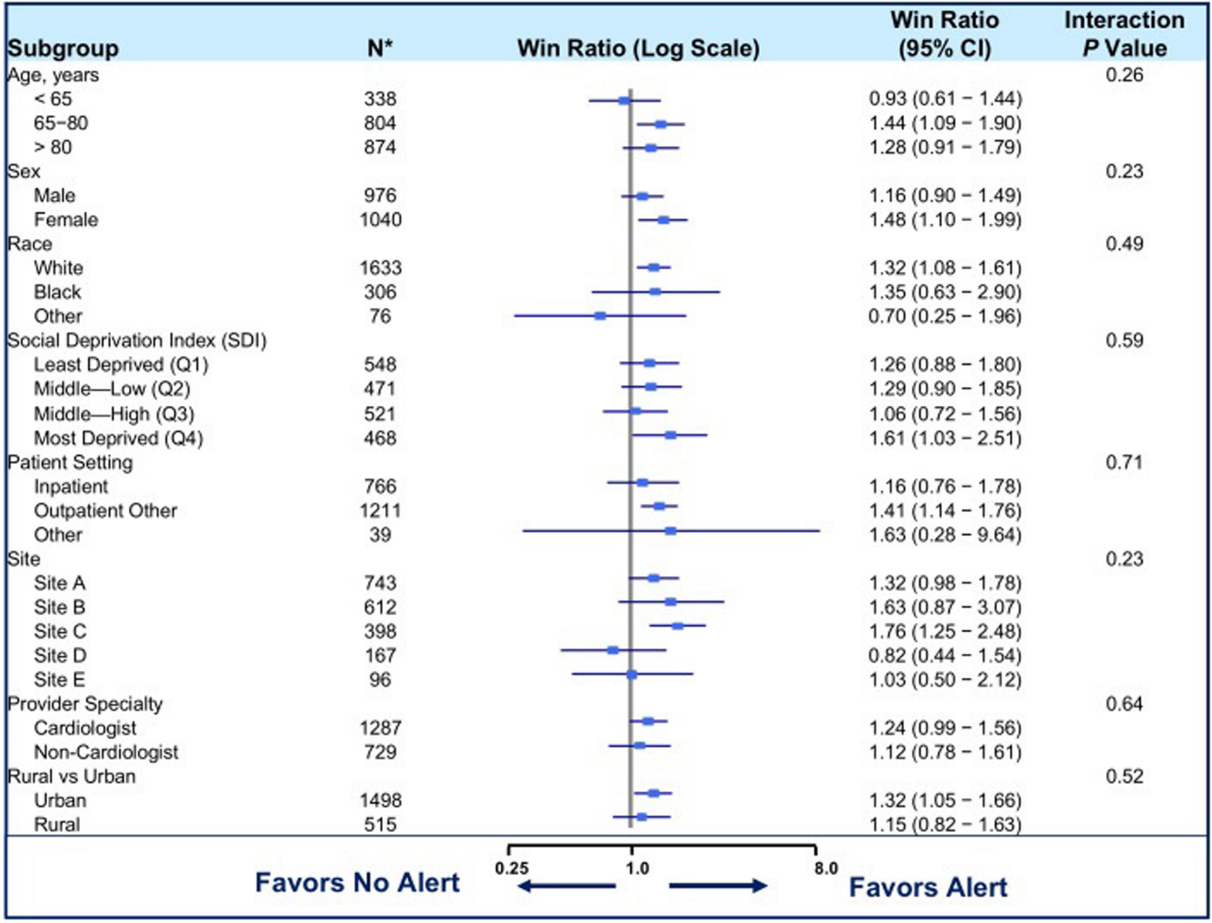
Figure 2. Schematic illustrating the hierarchical comparison used in the stratified win-ratio primary end point analysis, prioritizing time to valve intervention followed by time to multidisciplinary heart team (MHT) evaluation within 90 days.

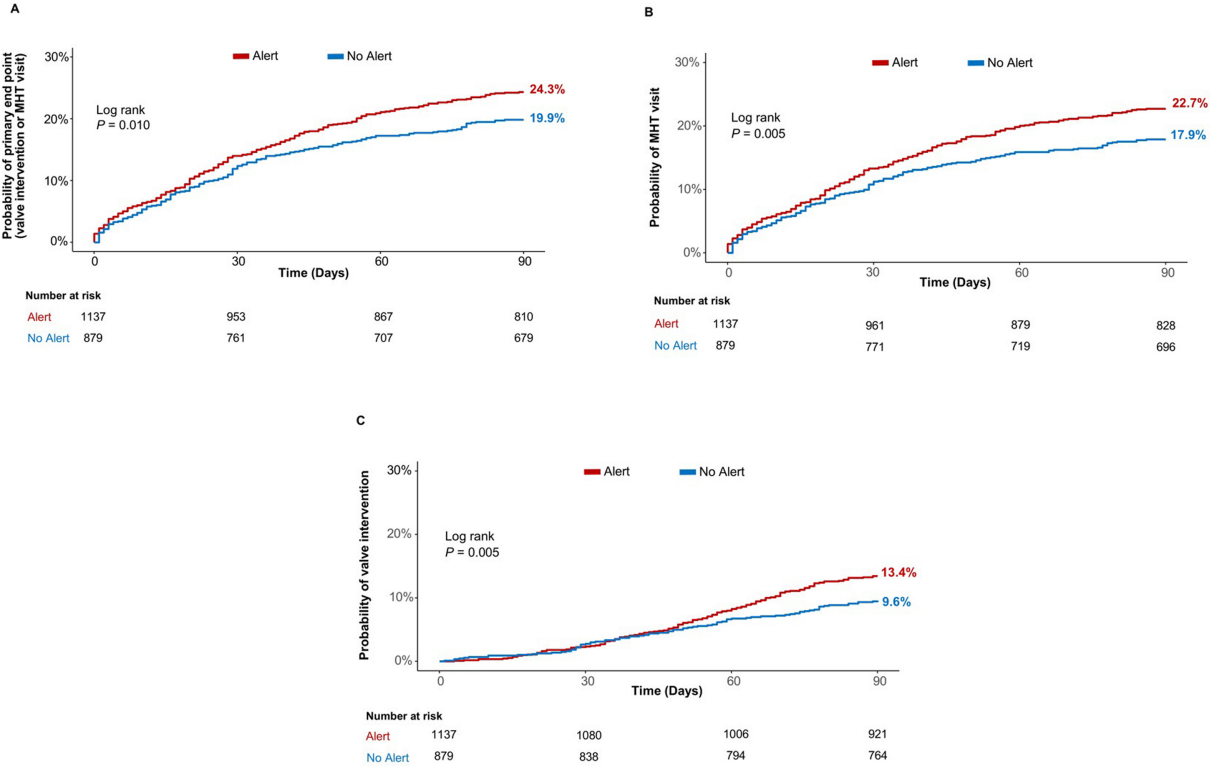
Figure 3. Forest plot displaying win ratios and 95% CIs for the primary hierarchical composite outcome across prespecified subgroups. N=number of echocardiograms.

Figure 4. Kaplan–Meier curves showing (A) time to the primary endpoint of valve intervention or multidisciplinary heart team (MHT) evaluation, (B) time to MHT visit, and (C) time to surgical or transcatheter valve intervention within 90 days in the modified intention-to-treat population.


Enrollment
Assessed for Eligibility
Hospitals = 35
Clinicians with an echo = 6,523
Echos = 147,122
Excluded 139,802 echos
- No criteria for significant AS or MR in the echo report.
Identified with Significant AS or MR
Clinicians with an echo = 1,741
Echos = 7,320
Excluded 5,042 echos
- Echo showed significant AS or MR but patient being managed by MHT, scheduled for MHT visit or VI, or had prosthetic valve.
Unmanaged Significant AS or MR
Clinicians with an echo = 914
Echos = 2,278
Excluded 160 echos (131 Clinicians)
- Echo ordered by a Clinician that opted out of study
Allocation
Randomized 1:1
(Clinicians = 783)
Analysis
ECN (Alert)
Clinicians = 394
Echos = 1,239
Intention-to-Treat (ITT) Population
Clinicians = 783
Echos = 2,118
Usual Care (No Alert)
Clinicians = 389
Echos = 879
Excluded 102 echos (18 Clinicians) for technical restrictions
- Alert not able to be presented in the site's EHR due to a technical restriction by the site.
ECN (Alert)
Clinicians = 376
Echos = 1,137
Patients =1,054
Modified Intention-to-Treat (mITT) Population
Clinicians = 765
Echos = 2,016
Patients = 1,905
Usual Care (No Alert)
Clinicians = 389
Echos = 879
Patients = 851
Excluded 363 echos for protocol deviations
- Patient in Alert arm whose provider did not receive an alert (failure to send;164 echos)
- Patient in the usual care arm whose provider received an alert (data contamination; 165 echos)
- Patient who was included in study but did not meet inclusion and exclusion criteria (34 echos)
ECN (Alert)
Clinicians = 332
Echos = 861
Per Protocol (PP) Population
Clinicians = 710
Echos = 1,653
Usual Care (No Alert)
Clinicians = 378
Echos = 792


Aortic Stenosis
705 x 550 = 387,750 pairs
Mitral Regurgitation
432 x 329 = 142,128 pairs
Alert Wins
Ties
No Alert Wins
1. Valve Intervention
First to transcatheter or surgical valve Intervention
51374
304790
31586
2. MHT Clinic Visit
First to visit with a member of the MHT Team
32156
239601
33033
Total Wins
83530
versus
64619
Win ratio (95% CI)
1.29 (1.01 - 1.65)
Alert Wins
Ties
No Alert Wins
13952
115505
12671
15368
89061
11076
29320
versus
23747
1.23 (0.90 - 1.69)
(P_{int}=.82)
Overall stratified win ratio: 1.27 (95% CI: 1.05 - 1.54), p=0.007


Subgroup
N*
Win Ratio (Log Scale)
Win Ratio (95% CI)
Interaction P Value
Age, years 0.26
< 65 338 0.93 (0.61 – 1.44)
65–80 804 1.44 (1.09 – 1.90)
> 80 874 1.28 (0.91 – 1.79)
Sex 0.23
Male 976 1.16 (0.90 – 1.49)
Female 1040 1.48 (1.10 – 1.99)
Race 0.49
White 1633 1.32 (1.08 – 1.61)
Black 306 1.35 (0.63 – 2.90)
Other 76 0.70 (0.25 – 1.96)
Social Deprivation Index (SDI) 0.59
Least Deprived (Q1) 548 1.26 (0.88 – 1.80)
Middle—Low (Q2) 471 1.29 (0.90 – 1.85)
Middle—High (Q3) 521 1.06 (0.72 – 1.56)
Most Deprived (Q4) 468 1.61 (1.03 – 2.51)
Patient Setting 0.71
Inpatient 766 1.16 (0.76 – 1.78)
Outpatient Other 1211 1.41 (1.14 – 1.76)
Other 39 1.63 (0.28 – 9.64)
Site 0.23
Site A 743 1.32 (0.98 – 1.78)
Site B 612 1.63 (0.87 – 3.07)
Site C 398 1.76 (1.25 – 2.48)
Site D 167 0.82 (0.44 – 1.54)
Site E 96 1.03 (0.50 – 2.12)
Provider Specialty 0.64
Cardiologist 1287 1.24 (0.99 – 1.56)
Non-Cardiologist 729 1.12 (0.78 – 1.61)
Rural vs Urban 0.52
Urban 1498 1.32 (1.05 – 1.66)
Rural 515 1.15 (0.82 – 1.63)
0.25
1.0
8.0
Favors No Alert
Favors Alert


A
Probability of primary end point (valve intervention or MHT visit)
30%
20%
10%
0%
Alert
No Alert
Log rank
P = 0.010
24.3%
19.9%
0
30
60
90
Time (Days)
Number at risk
Alert 1137 953 867 810
No Alert 879 761 707 679
B
Probability of MHT visit
30%
20%
10%
0%
Alert
No Alert
Log rank
P = 0.005
22.7%
17.9%
0
30
60
90
Time (Days)
Number at risk
Alert 1137 961 879 828
No Alert 879 771 719 696
C
Probability of valve intervention
30%
20%
10%
0%
Alert
No Alert
Log rank
P = 0.005
13.4%
9.6%
0
30
60
90
Time (Days)
Number at risk
Alert 1137 1080 1006 921
No Alert 879 838 794 764