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Authors

Loring, Zak
Shrader, Peter
Allen, Larry A
et al.

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Guideline-Directed Therapies for Comorbidities and Clinical Outcomes among Individuals with Atrial Fibrillation

Zak Loring, MD, MHS^{a,b}, Peter Shrader, MA^b, Larry A. Allen, MD, MHS^c, Rosalia Blanco, MS^b, Paul S. Chan, MD, MSc^d, Michael D. Ezekowitz, MB, ChB, DPhil^e, Gregg C. Fonarow, MD^f, James V. Freeman, MD, MPH, MS^g, Bernard J. Gersh, MB, ChB, DPhil^h, Kenneth W. Mahaffey, MDⁱ, Gerald V. Naccarelli, MD^j, Karen Pieper, MS^b, James A. Reiffel, MD^k, Daniel E. Singer, MD^l, Benjamin A. Steinberg, MD, MHS^m, Laine E. Thomas, PhD^b, Eric D. Peterson, MD, MPH^{a,b}, Jonathan P. Piccini, MD, MHS^{a,b}

^aDivision of Cardiology, Duke University Medical Center, Durham, NC

^bDuke Clinical Research Institute, Durham, NC

^cDivision of Cardiology, University of Colorado School of Medicine, Aurora, CO

^dDepartment of Cardiovascular Research, St Luke's Mid America Institute, Kansas City, MO

^eLankenau Institute for Medical Research, Wynnewood, PA

^fDepartment of Medicine, University of California, Los Angeles, CA

^gDepartment of Medicine, Yale University School of Medicine, New Haven, CT

^hDepartment of Medicine, Mayo Clinic College of Medicine, Rochester, MN

ⁱStanford Center for Clinical Research, Department of Medicine, Stanford University, Stanford, CA

^jSchool of Medicine, Penn State University, Hershey PA

^kVagelos College of Physicians and Surgeons, Columbia University, New York City, NY

^lHarvard Medical School and Massachusetts General Hospital, Boston, MA

^mUniversity of Utah, Salt Lake City, UT

Abstract

Background: Comorbidities are common in patients with atrial fibrillation (AF) and affect prognosis, yet are often under-treated. However, contemporary rates of use of guideline-directed therapies (GDT) for non-AF comorbidities and their association with outcomes is not well described.

Methods: We used the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) to test the association between GDT for non-AF comorbidities and major adverse cardiac or neurovascular events (MACNE- cardiovascular death, myocardial infarction, stroke/ thromboembolism, or new onset heart failure), all-cause mortality, new-onset heart failure and AF

progression. Adjustment was performed using Cox-proportional hazards models and logistic regression.

Results: Only 6,782 (33%) of the 20,434 patients eligible for one or more GDT for non-AF comorbidities received all indicated therapies. Use of all comorbidity-specific GDT was highest for patients with hyperlipidemia (75.6%) and lowest for diabetes mellitus (43.1%). Use of “all eligible” GDT was associated with a non-significant trend towards lower rates of MACNE (HR 0.90 [0.79–1.02]) and all-cause mortality (HR 0.90 [0.80–1.01]). Use of GDT for heart failure was associated with a lower risk of all-cause mortality (HR 0.77 [0.67–0.89]) and treatment of obstructive sleep apnea was associated with a lower risk of AF progression (OR 0.75 [0.62–0.90]).

Conclusion: In AF patients there is underuse of GDT for non-AF comorbidities. The association between GDT use and outcomes was strongest in heart failure and obstructive sleep apnea patients where use of GDT was associated with lower mortality and less AF progression.

Keywords

Atrial fibrillation; outcomes; guideline directed medical therapy

Introduction

Atrial fibrillation (AF) is an increasingly prevalent condition, which carries a substantial risk of stroke, heart failure, cognitive impairment, and mortality.^{1, 2} Comorbid conditions that carry additional cardiovascular risk are common among AF patients and are associated with higher rates of adverse outcomes.³ Many of these conditions have been associated with overall worsening of cardiac function,⁴ and progression of AF from paroxysmal to persistent forms.^{5, 6} Prior work has shown that the treatment of risk factors can improve outcomes in patients with AF and use of guideline directed therapies (GDT) for comorbid conditions can help reduce risk associated with these comorbidities.^{7–10} Yet, the majority of patients with AF do not receive all GDT for comorbid cardiovascular conditions for which they are eligible,¹¹ and the impact of receiving all eligible GDT use on clinical outcomes in AF patients is not well studied. We hypothesized that the use of all eligible GDT for comorbidities is associated with lower rates of adverse events among AF patients, as well as less progression of AF (from paroxysmal to persistent/permanent).

Methods

Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Patients from the Outcomes for Better Informed Treatment of AF (ORBIT-AF and ORBIT-AF II) registries were considered for inclusion in this study. The details of these registries have been previously published.^{12, 13} Briefly, the ORBIT-AF and ORBIT-AF II registries enrolled ambulatory, adult patients with electrocardiographically documented AF from outpatient US practices and followed them semiannually tracking clinical outcomes and events for a minimum of 2 years. ORBIT-AF enrolled 10,137 patients from 176 sites from June 29, 2010 through August 9, 2011. ORBIT-AF II enrolled 13,394 patients from 244 US sites from

February 20, 2013 through July 12, 2016. The study protocol was reviewed and approved by the Duke University Medical Center Institutional Review Board (IRB) and the IRB at each enrolling center. Primary funding was provided by Ortho-McNeil Janssen Scientific Affairs, LLC. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

For the purpose of this study, only patients with at least one of the following GDT eligible conditions (coronary artery disease [CAD], diabetes mellitus [DM], heart failure [HF], hyperlipidemia [HL], hypertension [HTN], peripheral vascular disease [PVD], or obstructive sleep apnea [OSA]) at baseline were included in this analysis. Additionally, patients were excluded if they did not have any available follow up data.

GDT Assessment

GDT eligibility was defined according to current professional guidelines published by the American College of Cardiology (ACC) and American Heart Association (AHA) and related professional societies for the management of CAD,¹⁴ DM,^{15, 16} HF,¹⁷ HL,¹⁶ HTN,¹⁵ PVD,¹⁸ and OSA.¹⁹ Specifically, GDT for CAD included use of a beta blocker, statin, angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) in the presence of DM or left ventricular ejection fraction (LVEF) < 40%, and an antiplatelet agent if the patient had a myocardial infarction (MI), percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) within the preceding 12 months. DM GDT included use of a statin and use of ACEi or ARB in the presence of CAD or LVEF < 40%. While glycemic control agents (e.g. insulin, metformin) are an important component of DM GDT, their use was not captured in the ORBIT registry and thus not included in the assessment of GDT for DM in this study. GDT for HF included use of a beta blocker, ACEi/ARB in the setting of LVEF < 40% or DM, aldosterone antagonist in the presence of New York Heart Association (NYHA) class II-IV symptoms and suitable creatinine level (< 2.5 mg/dL in men, < 2.0 mg/dL in women), and implantable cardioverter-defibrillator (ICD) in the presence of LVEF < 35% and NYHA class II-III symptoms. GDT for HL included use of a statin in the presence of CAD, DM, or PVD. GDT for HTN included use of an aldosterone antagonist, ACEi/ARB, calcium channel blocker, diuretic or beta blocker in the presence of previously diagnosed HTN or documented blood pressure > 140/90 (> 130/80 in patients with DM or chronic kidney disease). GDT for PVD required use of a statin. While antiplatelet agents are also indicated in patients with PVD, given the high use of anticoagulants in the ORBIT-AF cohorts which may influence antiplatelet use, we did not require use of antiplatelet therapy in our assessment of GDT for PVD in this study. Patients with OSA were considered to be on GDT if they reported use of a continuous positive airway pressure (CPAP) machine.

Because the number of therapies included in the GDT estimate varied by disease state (and consequently between patients), GDT use was analyzed across several different levels. The primary analysis was performed at the individual level with GDT as a binary variable (“All eligible” vs “Not all eligible”). GDT was evaluated as a binary variable because there was variance in both the number of comorbidities each patient had as well as the number of therapies considered as GDT for each comorbidity in this study (four of the seven evaluated

had only one therapy included as GDT). In addition, comorbidity-specific GDT use (also binary) was also assessed at an individual level to better understand how treatment of each comorbidity was associated with outcomes. Finally, GDT use was evaluated as a continuous variable (%GDT defined by [number of eligible therapies used] / [total number of eligible therapies]) at the site level to evaluate whether site-level treatment patterns had similar effects on outcomes as individual treatment effects.

Clinical Outcomes

The primary outcome of interest for this study was major adverse cardiac/neurovascular events (MACNE) including cardiovascular (CV) death, MI, embolic event (central nervous system or systemic) and new onset HF. Secondary outcomes included all-cause mortality, new onset HF, and AF progression from paroxysmal to persistent or from persistent to permanent (excluding patients with new-onset or permanent AF at baseline).

Statistical Analyses

Demographic and patient baseline characteristics were compared between patients who received “all eligible” GDT and those who received some or none of the GDT for which they were eligible (“not all eligible”). Variables following a Gaussian distribution were presented as mean \pm standard deviation; variables following non-Gaussian distributions were presented as median (interquartile range). Variables were compared using chi-square tests for categorical variables and the Wilcoxon rank sum test for continuous variables.

The relationship between all eligible GDT use and clinical outcomes was assessed with adjusted and unadjusted Cox-proportional hazard models for clinical outcomes and pooled logistic regression for AF progression (with site included as a random effect). Covariates included in the adjusted model are listed in the Appendix (Supplemental material) with analyses stratified across 128 combinations of comorbidities to account for number and type of comorbidity. All continuous variables were tested for linearity and any non-linear associations were accounted for using linear splines. A non-linear association was noted between the site level %GDT use and outcomes so a linear spline with a knot at 60% was used for site level analyses. At the patient level, a robust covariance estimate was included in order to account for within site correlation. Missingness was handled by 5 fold multiple imputation.²⁰ Analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Study Population

Of the 23,531 patients included in the combined ORBIT-AF and ORBIT-AF II registries, 2,446 patients were excluded for not having any of the conditions eligible for the GDT evaluated in this study, and an additional 651 patients did not have follow-up data resulting in a final study cohort of 20,434 patients. Table I shows the distribution of demographics, past medical history, baseline laboratory data and enrolling provider specialty stratified by patients being on all eligible GDT (“all eligible”) vs some or none of the GDT for which they were eligible (“not all eligible”). The mean age was 72.3 ± 10.8 years, 41.7% were

female, and 87.1% were white. A total of 6,782 (33.2%) patients were on all GDT for which they were eligible; whereas 13,652 (66.8%) were on some or none of their eligible GDT. Patients in the “not all eligible” group were more frequently black (5.8% vs 4.0%, $p<0.001$) and/or Hispanic (5.0% vs 4.5%, $p<0.001$) and were more commonly insured by Medicare or Medicaid (57.3% vs 53.4%, $p<0.001$). Of the cardiovascular comorbidities with treatments included in our assessment of GDT, patients in the “not all eligible” group more frequently had five of the seven studied comorbidities: CAD (38.8% vs 25.0%), DM (40.0% vs 12.3%), HF (33.4% vs 21.2%), PVD (13.3% vs 8.0%), and OSA (23.1% vs 13.2%) ($p<0.001$ for all). Evaluating total number of GDT-eligible comorbidities, patients in the “not all eligible” group had a median of 3 (2–4) GDT-eligible comorbidities compared to 2 (2–3) in patients on “all eligible” therapies ($p<0.001$). Patients in the “not all eligible” group also more commonly had a medical history of non-GDT related conditions including thyroid disease, COPD, anemia, prior stroke or transient ischemic attack, GI bleed, liver disease, and dialysis. More patients in the “not all eligible” group had frailty (defined as three or more of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed or low physical activity) compared to the “all eligible” group (5.3% vs 3.4%, $p<0.001$). CHA₂DS₂VASC scores were higher in patients in the “not all eligible” group (4 [3–5] vs 3 [2–4], $p<0.001$) yet these patients had slightly lower rates of oral anticoagulation use (84.1% vs 85.5%, $p=0.01$).

Clinical Outcomes by Total GDT Use

Over the study period, there were 1,678 MACNE events (5.0 events per 100 patient years [event rate]), and 1,809 deaths (event rate = 5.2). A total of 419 patients developed new onset HF (event rate 1.8). Of the 11,238 patients with paroxysmal or persistent AF, 2,738 (24.4%) progressed to persistent or permanent AF over the course of follow up.

The association between use of “all eligible” GDT vs “not all eligible” GDT is shown in Figure 1. While there was an association between use of “all eligible” GDT and lower risk of MACNE (HR 0.84 [0.75–0.95]) in the unadjusted models, there was no association between “all GDT” use and these outcomes in the fully adjusted models. There were trends towards lower rates of MACNE and all-cause mortality (HR 0.90 [0.79–1.02], $p=0.09$ and HR 0.90 [0.80–1.01], $p=0.08$ respectively), but these did not reach statistical significance.

Comorbidity Specific GDT Use and Clinical Outcomes

In the study cohort, there were 6,990 patients with CAD, 6,294 patients with DM, 6,001 patients with HF, 14,601 with HL, 18,474 patients with HTN, 2,358 patients with PVD, and 4,045 patients with OSA. Use of each GDT by comorbidity is shown in Table II and Figure 2. Among CAD patients, usage was highest for antiplatelet agents (75.0%), beta blockers (73.5%), and statins (73.1%) and lowest for ACEi/ARB (63.7%). Use of all eligible CAD related GDT was substantially lower than any individual agent (45.0%). Similarly, among diabetic patients, use of ACEi/ARBs and statins were relatively high (60.7% and 65.9% respectively) compared to the number of patients on all eligible DM related GDT (43.1%). For patients with HF, there was high use of beta blockers (76.4%) and ACEi/ARBs (65.2%), lower for ICDs (45.3%) and lowest for aldosterone antagonists (16.4%). Use of all eligible HF related GDT was 47.0%. HL, HTN, PVD and OSA all had single therapies considered as

GDT in this analysis. Most patients eligible for these therapies received them; 75.6% of hyperlipidemia patients and 67.3% of PVD were on a statin, 54.1% of hypertensive patients were on an antihypertensive, 57.7% of OSA patients used CPAP. Of patients eligible for beta blocker by any indication, 73.5% were on treatment. Similarly, 62.2% of patients eligible for ACEi/ARB and 67.0% of patients eligible for statins by any indication were on treatment.

The association between the use of “all eligible” vs “not all eligible” comorbidity specific GDT and outcomes is shown in Figure 3. None of the comorbidity specific GDT were associated with the primary endpoint (MACNE). For the end point of all-cause mortality, use of all eligible HF related GDT was associated with a lower hazard of mortality (HR 0.77 [0.67–0.89], $p < 0.001$). Use of all CAD related GDT was associated with a higher odds of AF progression (OR 1.17 [1.01–1.34]). Use of CPAP for OSA was associated with a lower odds of AF progression (OR 0.75 [0.62–0.90]). Use of all GDT for DM, HL HTN and PVD was not associated with any of the outcomes.

Site level analyses

A total of 322 sites were included in this analysis including 199 cardiology practices, 62 internal medicine/primary care practices, 60 electrophysiology practices and 1 neurology practice. The mean %GDT at the site level was $59.9 \pm 9.5\%$ and was similar across site types (60.1% for cardiology, 56.7% for internal medicine/primary care, 62.2% for electrophysiology, and 67.0% for neurology). The association between site level %GDT use and outcomes is shown in the Supplemental Table. There was a non-linear relationship between site level %GDT use and outcomes so a linear spline was used and results were derived separately for sites with %GDT above and below 60% (the approximate level where risk changed, which also corresponds with the mean value). At low utilizing sites (sites with %GDT below the mean), increasing %GDT use was associated with a higher hazard of MACNE (adjusted HR 1.37, 95% confidence interval [CI] 1.15–1.64 per 10% increase), and new onset HF (adjusted HR 1.71 [1.14–2.58]). There were no statistically significant relationships between increasing %GDT and clinical outcomes at high utilizing sites (sites with %GDT above the mean); however, there was a trend towards lower hazards of all-cause mortality (HR 0.89 [0.77–1.03] per 10% increase) with higher %GDT use.

Discussion

In this analysis of a large nationwide registry of patients with atrial fibrillation, receiving all eligible GDT was infrequently achieved. Only 33% of patients received all the GDT for which they were eligible. Patients who received “all eligible” GDT were more often white and had fewer of the evaluated comorbidities. Comorbidity specific GDT use was highest for patients with HL (75.6% of patients appropriately treated with a statin) and similar to rates reported in other outpatient registries.^{21, 22} Comorbidity specific GDT use was lowest for patients with DM (43.1% of patients on all eligible diabetic therapies), but the rates of statin and ACEi/ARB use were similar to large registry studies.^{23, 24} When examining individual comorbidities, use of HF related GDT was associated with a 23% lower hazard of all-cause mortality and use of CPAP in OSA patients was associated with a 25% lower odds of AF

progression. Use of CAD related GDT was associated with a higher hazard of AF progression.

Concurrent comorbidities and risk factors are common in AF and contribute to the risk of adverse outcomes associated with AF.^{25, 26} Prior work, such as the ARREST-AF Cohort Study,¹⁰ has demonstrated that aggressive management of risk factors such as blood pressure, weight, cholesterol, glycemic control, sleep apnea and use of alcohol and/or tobacco can result in improved AF control and less symptom burden than standard care. Yet, two thirds of the AF patients in this study were not receiving all the GDT for which they were eligible. We also found that a lower proportion of African American patients received “all eligible” GDT compared to whites. This may be due to an overall higher burden of disease (patients in the “all eligible” GDT group had fewer of the comorbidities evaluated) or a manifestation of racial disparities in cardiovascular care.²⁷ This highlights the importance of quality improvement efforts like Get With The Guidelines- AFIB which aim to assist hospitals in providing up to date evidence based treatment for AF patients.²⁸

The relationship between GDT use and clinical outcomes is influenced both by the type of patients who received GDT as well as the direct effect of GDT on outcomes. While patients receiving “all eligible” GDT had a trend towards lower hazards of MACNE or all-cause mortality, we also found that these patients had fewer of the evaluated comorbidities than those on “not all eligible” therapies. The association between GDT use and outcomes is likely influenced in part by confounding if the lower event rates among patients on “all eligible” GDT was reflective of their lower overall disease burden rather than an effect of the therapies themselves. To explore this further, we evaluated the use of GDT at the site level and found that at low utilizing sites (sites where GDT was used in 60% of situations in which it was indicated), GDT use was associated with higher hazard of MACNE, major bleeding, all-cause and CV hospitalization as well as new onset HF. It is possible that at these sites, the studied therapies were allocated only to patients with high disease severity and thus GDT use was associated with higher rates of adverse outcomes. In high utilizing sites, where GDT use was likely more uniformly used across patient risk groups, there was a trend towards lower all-cause mortality and bleeding hospitalizations. The consistency of the relationship across analyses suggests a more direct relationship between GDT use and all-cause mortality; however any causal relationship cannot be inferred from this observational analysis.

The comorbidity specific analyses provide a more detailed look into the drivers behind the relationships between GDT use and clinical outcomes. Use of HF related GDT was associated with 23% lower hazards of all-cause mortality. This is consistent with previously published estimates of the reduction in mortality risk attributable to heart failure therapies ranging from 17% for ACEi/ARB to 34% for beta blockers.²⁹ Despite the aggregate evidence for the benefit of GDT in HF, it is notable that our data estimate that for patients with HF and AF, 24% of eligible patients are not on a BB, 35% of eligible patients are not on an ACEi or ARB, and 55% of eligible patients do not have an ICD. These rates are similar to the general HF population in whom underuse of GDT and device therapy among eligible patients has been well documented.^{30, 31} We also observed that CPAP use among

OSA patients was associated with a lower odds of AF progression, which is consistent with prior analyses.^{32, 33}

The association of CAD related GDT use with AF progression is less straightforward. CAD related GDT included beta blocker, statin and in some patients ACEi/ARB and an antiplatelet agent. Many of these therapies were components of GDT for other evaluated comorbidities (beta blockers and ACEi/ARB were components of HF related GDT and statin use was considered HL GDT) none of which were associated with AF progression. While this may be due to a unique relationship between these medications and AF progression in the setting of CAD, the association may also be due to chance.

The results of this study highlight a need for improved implementation of GDT for AF patients. An integrated management approach to atrial fibrillation that incorporates nurse-based, physician supervised clinic model has been shown to be cost-effective and may reduce cardiovascular morbidity and mortality.^{34, 35} This approach may provide the ideal platform for optimizing both direct AF care as well as improve the implementation of all eligible GDT for comorbidities in AF patients both of which may improve clinical outcomes.

Limitations:

This study included patients who were part of a voluntary registry and may not be fully representative of all AF patients or patterns of care in the US. Not all guideline recommended therapies were measured in this registry (including use of hydralazine/nitrates, angiotensin receptor-neprilysin inhibitors, or cardiac resynchronization therapy) nor were non-pharmacologic/device based interventions such as smoking cessation, diet and exercise evaluated. ACC/AHA Guidelines for the management of heart failure were updated in 2013 during the study period and expanded the class I recommendation for aldosterone antagonists in HF to include patients with NYHA class II symptoms.³⁶ We chose to consider patients with HF and NYHA class II-IV symptoms as eligible for aldosterone antagonists as the pivotal trial prompting this expansion (EMPHASIS-HF)³⁷ was presented in 2010 and published in 2011 near the beginning of the study period, which may have overestimated the number of patients eligible for aldosterone antagonists based on published guidelines. CPAP use for OSA was included as a component of GDT as part of the hypothesis that evidence-based therapies may reduce AF progression; however, there is no robust evidence that CPAP use for OSA improves cardiovascular outcomes and thus its inclusions as a component of GDT for the MACNE, mortality and new-onset heart failure endpoints may have biased those analyses towards the null.³⁸ As mentioned above, patients “not all eligible” category were older with greater comorbidity. Our analyses were stratified on both the type and number of comorbid conditions to compare patients with similar risk profiles and attempt to isolate the effect of GDT use on outcomes. However, this statistical technique is unable to account for unmeasured confounding factors nor the severity of each of these conditions. Thus some component of the trend towards worse outcomes in the “undertreated” patients may reflect the greater overall illness burden in this group. While medication use was documented, adherence and dosing information was not available. Additionally, information about contraindications or intolerances to the therapies evaluated in this study was not

available. Comorbidity presence and medication use was assessed at the time of registry enrollment; thus, the development of comorbid conditions or starting/stopping of GDT after registry enrollment are not accounted for in the presented models and would have biased the result towards the null. Registry patients may be more likely to receive GDT than the general population due to their more frequent contact with the health system so estimates of GDT use in the general population may be lower than reported here. Finally, the retrospective, observational nature of this study limits any causal inference and may be impacted by residual, unmeasured confounding.

Conclusions

GDT for treatment of comorbidities in AF patients in routine practice is under-utilized. The association between receiving all eligible GDT use and clinical outcomes was strongest in those with HF and OSA, where use of GDT was associated with lower all-cause mortality and less AF progression, respectively. Future efforts to improve the comprehensive care of AF patients including management of their comorbid conditions may improve clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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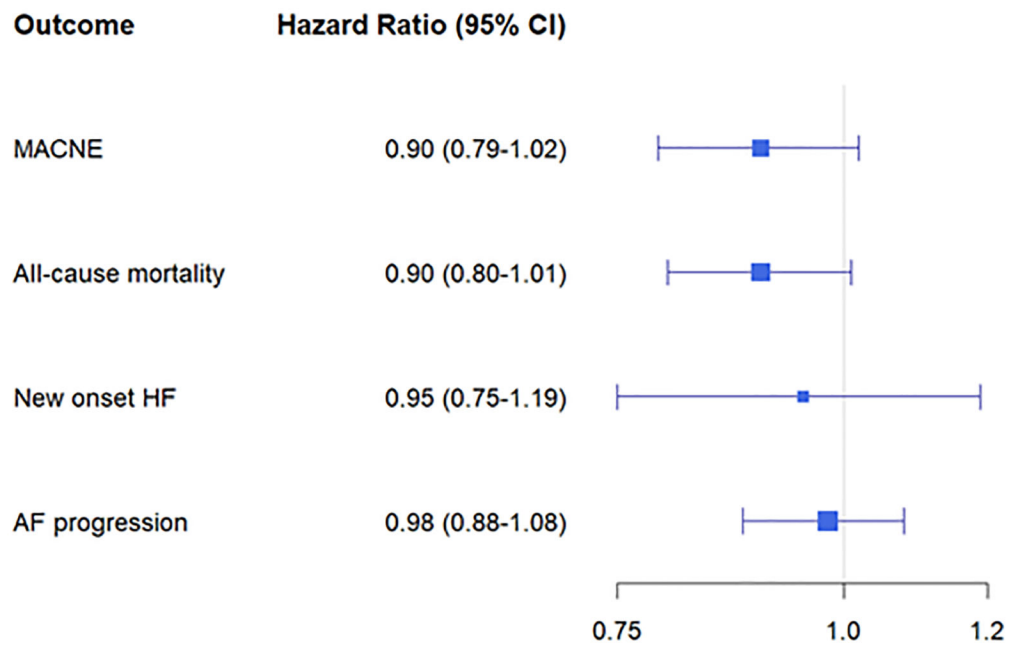


Figure 1:
 Association between use of “all eligible” GDT and clinical outcomes. Abbreviations AF = atrial fibrillation; HF = congestive heart failure; CV = cardiovascular; MACNE = major adverse cardiac/neurovascular events.

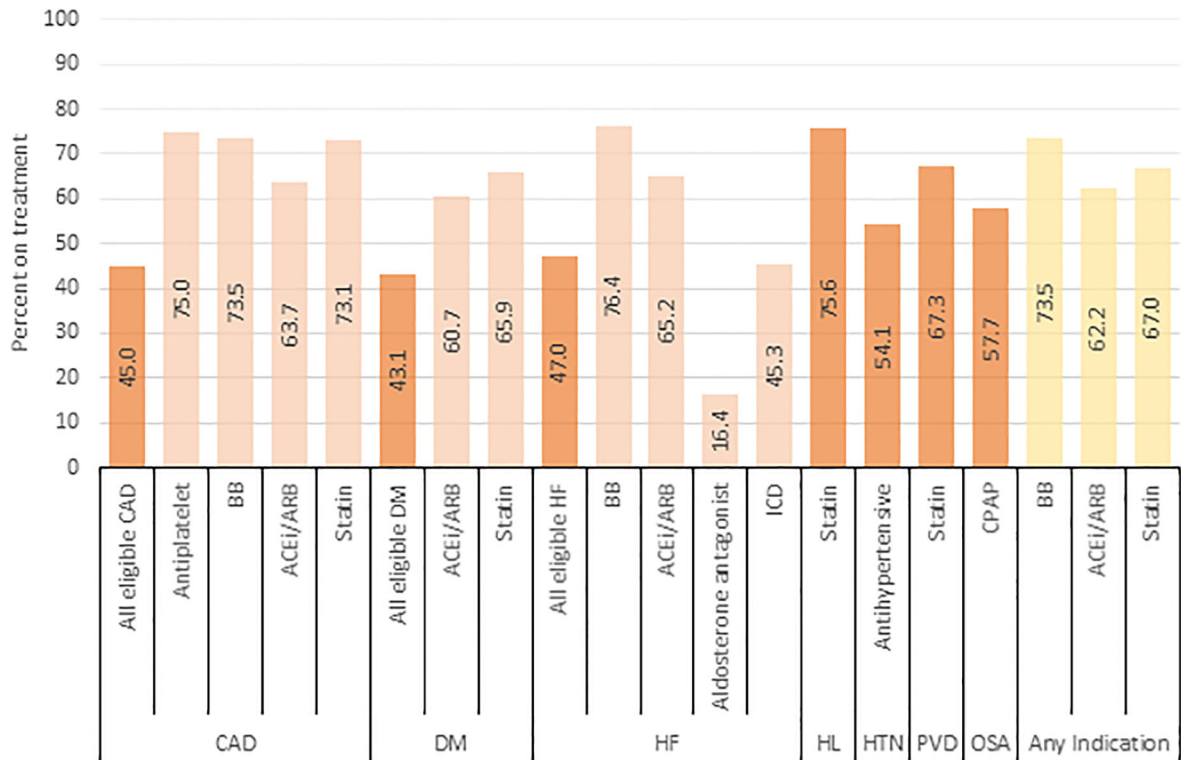


Figure 2:

GDT use by comorbidity. Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB=beta blocker; CAD = coronary artery disease; HF = congestive heart failure; CPAP = continuous positive airway pressure; DM = diabetes mellitus; HL = hyperlipidemia; HTN = hypertension; ICD = implantable cardioverter defibrillator; OSA= obstructive sleep apnea; PVD = peripheral vascular disease.

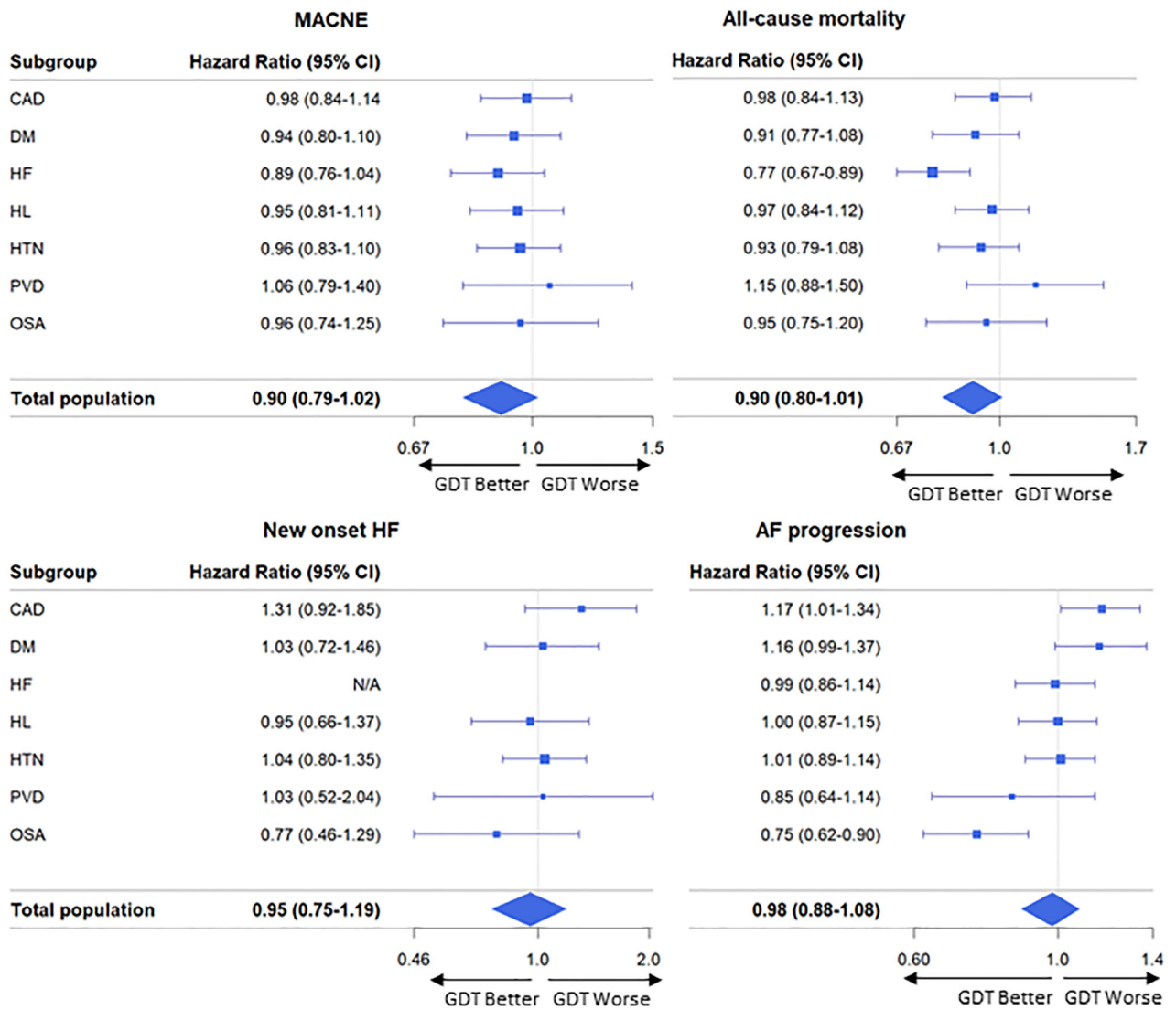


Figure 3: Comorbidity-specific GDT use and MACNE (upper left): all-cause mortality (upper right): new onset HF (lower left), and AF progression (lower right). Abbreviations: MACNE = Major adverse cariac/neurovascular events; CI= confidence interval; CAD = coronary artery disease; DM = diabetes mellitus; HF = heart failure; HL = hyperlipidemia; HTN = hypertension; PVD = peripheral vascular disease; OSA = obstructive sleep apnea; GDT = guideline-directed therapies.

Table 1:

Patient characteristics by use of “all eligible” or “not all eligible” GDT.

	Overall	“Receiving all eligible”	“Not receiving all eligible”	P-Value
N	20,434	6,782	13,652	
Age, yrs	72.3 ± 10.8	71.8 ± 10.8	72.6 ± 10.7	<0.001
Sex (n, % female)	8523 (41.7%)	2782 (41.0%)	5741 (42.0%)	0.16
Race				<0.001
White	17794 (87.1%)	6022 (88.8%)	11772 (86.3%)	
Black/African American	1071 (5.3%)	274 (4.0%)	797 (5.8%)	
Asian	256 (1.3%)	80 (1.2%)	176 (1.3%)	
American Indian/Alaska Native	57 (0.3%)	17 (0.2%)	40 (0.3%)	
Hispanic	987 (4.8%)	308 (4.5%)	679 (5.0%)	
Native Hawaiian/Pacific Islander	20 (0.1%)	10 (0.2%)	10 (0.1%)	
Other	234 (1.2%)	69 (1.0%)	165 (1.2%)	
Missing	15 (0.1%)	2 (<0.1%)	13 (0.1%)	
Insurance				<0.001
Medicare or Medicaid	11454 (56.0%)	3624 (53.4%)	7830 (57.3%)	
Private	7941 (38.9%)	2804 (41.4%)	5137 (37.6%)	
Cardiovascular comorbidities and risk factors				
Total number of GDT-eligible comorbidities	3 (2-4)	2 (2-3)	3 (2-4)	<0.001
Coronary artery disease	6990 (34.2%)	1692 (25.0%)	5298 (38.8%)	<0.001
Diabetes mellitus	6294 (30.8%)	835 (12.3%)	5459 (40.0%)	<0.001
Heart failure	6001 (29.4%)	1438 (21.2%)	4563 (33.4%)	<0.001
Hyperlipidemia	14601 (74.4%)	4863 (71.7%)	9738 (71.3%)	0.58
Hypertension	18474 (90.4%)	6123 (90.3%)	12351 (90.5%)	0.67
Peripheral vascular disease	2358 (11.5%)	543 (8.0%)	1815 (13.3%)	<0.001
Obstructive sleep apnea	4045 (19.8%)	894 (13.2%)	3151 (23.1%)	<0.001
Other medical history				
Cancer	4437 (21.7%)	1455 (21.4%)	2982 (21.8%)	0.52
Thyroid disease	4051 (19.8%)	1233 (18.2%)	2818 (20.6%)	<0.001
COPD	2930 (14.3%)	768 (11.3%)	2162 (15.8%)	<0.001

	Overall	“Receiving all eligible”	“Not receiving all eligible”	P-Value
Anemia	2921 (14.3%)	788 (11.6%)	2133 (15.6%)	<0.001
Prior stroke or transient ischemic attack	2697 (13.2%)	771 (11.4%)	1926 (14.1%)	<0.001
Frailty	949 (4.7%)	229 (3.4%)	720 (5.3%)	<0.001
GI bleed	1391 (6.8%)	387 (5.7%)	1004 (7.4%)	<0.001
Cognitive impairment/Dementia	468 (2.3%)	146 (2.2%)	322 (2.4%)	0.35
Liver disease	442 (2.2%)	123 (1.8%)	319 (2.3%)	0.02
Dialysis	237 (1.2%)	46 (0.7%)	191 (1.4%)	<0.001
CHA ₂ DS ₂ VASC Score	4 (3–5)	3 (2–4)	4 (3–5)	<0.001
On oral anticoagulation	17285 (84.6%)	5799 (85.5%)	11486 (84.1%)	0.01
Laboratory data, median (IQR)				
eGFR (ml/min/1.73 m ²)	69.7 (55.4–85.3)	73.6 (61.6–87.0)	67.1 (52.3–84.0)	<0.001
Hemoglobin (g/dL)	13.5 (12.2–14.7)	13.7 (12.5–14.8)	13.4 (12.1–14.6)	<0.001
Provider specialty				
Cardiology	13929 (68.2%)	4625 (68.2%)	9304 (68.2%)	
Electrophysiology	3775 (18.5%)	1318 (19.4%)	2457 (18.0%)	
Internal medicine/Family practice	2646 (13.0%)	802 (11.8%)	1844 (13.5%)	

COPD = chronic obstructive lung disease; eGFR = estimated glomerular filtration rate; GDT = guideline directed medical therapy; IQR = interquartile range

GDT use by comorbidity. Number and percent of patients receiving the components of GDT for each comorbidity.

Table II:

GDT use by comorbidity	Eligible	On Treatment	% On Treatment
CAD			
Antiplatelet agent	993	745	75.0%
Beta blocker	6990	5137	73.5%
ACEi/ARB	3447	2196	63.7%
Statin	6990	5109	73.1%
Taking all eligible therapies	6990	3145	45.0%
Diabetes mellitus			
ACE/ARB	6294	3818	60.7%
Statin	6294	4150	65.9%
Taking all eligible therapies	6294	2711	43.1%
Heart failure			
Beta blocker	6001	4584	76.4%
ACEi/ARB	3509	2288	65.2%
Aldosterone antagonist	1142	187	16.4%
ICD	1119	507	45.3%
Taking all eligible therapies	6001	2822	47.0%
Hyperlipidemia			
Statin	9282	7020	75.6%
Hypertension			
Antihypertensive	18474	9991	54.1%
PVD			
Statin	2358	1587	67.3%
Obstructive sleep apnea			
CPAP	4045	2333	57.7%

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; CAD = coronary artery disease; HF = heart failure; CPAP = continuous positive airway pressure; ICD = implantable cardioverter defibrillator; OSA = obstructive sleep apnea; PVD = peripheral vascular disease.