Referral for Specialist Follow-up and Its Association With Post-discharge Mortality Among Patients With Systolic Heart Failure (from the National Heart Failure Audit for England and Wales)

Connor A. Emdin, DPhil[a], Allan J. Hsiao, MPhil[b], Amit Kiran, PhD[a], Nathalie Conrad, MSc[a], Gholamreza Salimi-Khorshidi, DPhil[a], Mark Woodward, PhD[a,c], Simon G. Anderson, PhD[a], Hamid Mohseni, PhD[a], John J.V. McMurray, DM[d], John G.F. Cleland, MD[e], Henry Dargie, MB, ChB[d], Suzanna Hardman, PhD[f], Theresa McDonagh, MD[g], and Kazem Rahimi, MD, MSc[a,h,*]

For patients admitted with worsening heart failure (HF), early follow-up after discharge is recommended. Whether outcomes can be improved when follow-up is done by cardiologists is uncertain. We aimed to determine the association between cardiology follow-up and risk of death for patients with HF discharged from hospital. Using data from the National Heart Failure Audit (England and Wales), we investigated the effect of referral to cardiology follow-up on 30-day and 1-year mortality in 68,772 patients with HF and a reduced left ventricular ejection fraction discharged from 185 hospitals from 2007 to 2013. The primary analyses used instrumental variable analysis complemented by hierarchical logistic and propensity-matched models. At the hospital level, rates of referral to cardiologists varied from 6% to 96%. The median odds ratio (OR) for referral to cardiologist was 2.3 (95% confidence interval [CI] 2.1 to 2.5), suggesting that, on average, the odds of a patient being referred for cardiologist follow-up after discharge differed ~2.3 times from one randomly selected hospital to another one. Based on the proportion of patients (per region) referred for cardiology follow-up, referral for cardiology follow-up was associated with lower 30-day (OR 0.70; 95% CI 0.55 to 0.89) and 1-year mortality (OR 0.81; 95% CI 0.68 to 0.95) compared with no plans for cardiology follow-up (i.e., standard follow-up done by family doctors). Results from hierarchical logistic models and propensity-matched models were consistent (30-day mortality OR 0.66; 95% CI 0.61 to 0.72 and 0.66; 95% CI 0.58 to 0.76 for hierarchical and propensity matched models, respectively). For patients with HF and a reduced left ventricular ejection fraction admitted to hospital with worsening symptoms, referral to cardiology services for follow-up after discharge is strongly associated with reduced mortality, both early and late. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (Am J Cardiol 2017;119:440−444)

In the United Kingdom's health care system, cardiology care is generally provided by the hospitals and, hence, any policy recommendation for routine cardiology follow-up would have major resource and organizational implications for those hospital staff and payers not currently providing this component. We sought to assess this policy recommendation by investigating the effect of referral to cardiology follow-up on the risk of 30-day and 1-year mortality in a large cohort of patients admitted for heart failure and a reduced left ventricular ejection fraction (HFREF) in England and Wales.

Methods

This study is a part of the Understanding National Variation and Effects of Interventions at different Levels of Care for Heart Failure (UNVEIL-CHF) study, which aims to characterize variation in care and outcomes for patients hospitalized for heart failure (HF) from 2007 to 2013 and enrolled in the National Heart Failure Audit for England and Wales.[1] Only hospital admissions in which the patient survived to discharge were eligible for inclusion in the study. We restricted our analysis to patients with HFREF (an ejection fraction <40% or evidence of left ventricular systolic dysfunction) because clearly defined and evidence-based treatment recommendations exist only for this subgroup of patients with HF. For patients with >1 hospital

Table 1
Selected baseline characteristics by referral for cardiologist follow-up

	Overall Cohort			Propensity Matched Cohort		
	Follow Up (n = 40,769)	No Follow Up (n = 28,003)	Standardized Difference	Follow Up (n = 11571)	No Follow Up (n = 11571)	Standardized Difference
Predicted one year mortality (HF severity)*	25.5%	32.0%	52.7%	28.2%	28.3%	0.8%
Age (years)						
<60	17.9%	6.5%	35.5%	10.8%	11.0%	0.7%
60-80	52.9%	39.3%	27.6%	51.4%	50.5%	1.7%
>80	29.2%	54.2%	52.6%	37.8%	38.4%	1.3%
Women	32.4%	42.5%	21.0%	64.3%	64.4%	0.1%
NYHA Class						
I	6.3%	6.6%	1.2%	6.5%	6.6%	0.2%
II	19.3%	16.8%	6.5%	18.4%	18.3%	0.2%
III	45.9%	44.5%	2.8%	45.2%	45.5%	0.6%
IV	28.6%	32.2%	7.9%	29.9%	29.7%	0.6%
Peripheral Oedema						
None	31.1%	24.9%	13.7%	28.3%	28.1%	0.4%
Mild	26.3%	25.6%	1.6%	26.2%	25.9%	0.7%
Moderate	28.7%	32.5%	8.3%	30.2%	30.5%	0.7%
Severe	14.0%	17.0%	8.2%	15.3%	15.4%	0.4%
Diabetes mellitus	30.0%	29.4%	1.2%	31.0%	30.9%	0.1%
Hypertension	50.6%	51.8%	2.4%	51.3%	51.0%	0.7%
Coronary Heart Disease	51.4%	51.3%	0.4%	52.8%	52.6%	0.3%
Valve Disease	19.7%	18.4%	3.3%	18.9%	19.0%	0.3%
Baseline ECG						
Atrial fibrillation	36.9%	44.3%	15.3%	39.5%	39.9%	0.6%
Left bundle branch block	12.8%	11.5%	4.0%	12.2%	12.2%	0.1%
Previous Myocardial Infarction	2.2%	1.7%	4.1%	1.9%	2.0%	0.3%
Baseline ECHO						
Diastolic dysfunction	1.1%	1.0%	0.6%	1.0%	1.0%	0.5%
Left ventricular hypertrophy	0.9%	1.3%	4.2%	1.0%	1.0%	0.4%
Valve disease	5.4%	6.1%	2.9%	5.7%	5.4%	1.0%
Treated on Cardiology Ward	70.4%	38.2%	68.3%	59.0%	59.0%	0.1%
Therapies						
ACE/ARB	84.6%	73.6%	27.3%	81.2%	81.2%	0.2%
Beta-blocker	77.6%	64.2%	30%	73.1%	73.3%	0.6%

ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin-receptor blocker; ECG = electrocardiogram; ECHO = echocardiogram; HF = heart failure; NYHA = New York Heart Association.

* Logistic regression, adjusted for age, sex, breathlessness, peripheral edema, history of diabetes, history of ischemic heart disease, history of hypertension, history of valve disease, atrial fibrillation, left bundle branch block, previous myocardial infarction, diastolic dysfunction, left ventricular hypertrophy and valve disease, used to predict the likelihood of death within one year.

admission (10,280, 14.4%), we randomly selected 1 admission. Our exposure was referral for cardiology follow-up after discharge from the hospital. Follow-up started from the date of discharge and was censored at death or the end of follow-up (March 2013). Two primary outcomes, 30-day and 1-year mortality, were used. As longer term (>6 months) follow-up was not available for subjects admitted in 2012/2013, the analyses of 1-year mortality was restricted to 2007 to 2011. The analyses of 30-day mortality were from 2007 until March 2013.

Because findings from nonrandomized comparisons are commonly subject to confounding, our primary analysis was based on a quasi-randomized design using an instrumental variable approach.[2] A valid instrument is correlated with the treatment of interest (referral to cardiology follow-up) but is not correlated with the outcome of interest (30-day and 1-year mortality), except through the treatment of interest.[3] We, thus, used regional variation in referral to cardiology follow-up, that is, the proportion of patients referred for

cardiology follow-up in a given region, as our instrumental variable. The instrument was validated by classifying regions into fifths, to examine whether prognostic factors related to mortality are similar across regions and to demonstrate that it is unlikely that regional variation in cardiology referral would affect mortality other than through difference in rates of referral to cardiology follow-up.[2] Two-stage least-square logistic regression with robust SEs was then used to estimate the causal effect of referral for cardiology follow-up on 30-day and 1-year mortality.

In addition, we conducted 2 complementary statistical techniques to ensure that findings from our main analysis are robust to our design and modeling assumptions.[4] First, hierarchical logistic models were used to examine the association between referral to cardiology follow-up and risk of 30-day and 1-year mortality, adjusting for 34 covariates: age, gender, New York Heart Association class I, II, III, or IV, peripheral edema (none, mild, moderate, or severe), history of diabetes, history of ischemic heart disease, history of

Table 2
Selected patient characteristics across the fifths of cardiology referral for follow-up at regional levels

	Quintile of Regional Referral to Cardiology Follow Up Rates				
	Q1 (4.6-43.7)	Q2 (43.7-54.3)	Q3 (54.7-63.7)	Q4 (64.2-74.0)	Q5 (75.0-100)
Number of patients*	13539	13444	13977	13351	14461
Cardiology Referral Rate	34.4%	49.2%	59.1%	69.2%	83.0%
Predicted one year mortality (HF severity)	29.4%	28.7%	28.1%	27.5%	26.8%
Age (years)					
<60	10.4%	12.0%	13.4%	14.5%	15.9%
60-80	45.4%	45.8%	47.0%	48.1%	50.3%
>80	44.2%	42.2%	39.6%	37.4%	33.8%
Women	39.1%	37.1%	36.9%	35.5%	34.0%
NYHA Class					
I	8.1%	7.0%	6.2%	5.5%	5.2%
II	16.4%	17.4%	18.0%	19.1%	20.3%
III	42.6%	44.3%	46.5%	47.8%	45.5%
IV	32.9%	31.3%	29.3%	27.6%	29.0%
Peripheral Edema					
None	28.8%	29.3%	28.3%	27.9%	28.6%
Mild	24.1%	25.4%	26.2%	27.2%	26.9%
Moderate	30.6%	29.9%	30.2%	30.1%	30.2%
Severe	16.5%	15.4%	15.3%	14.8%	14.3%
Diabetes mellitus	27.6%	29.2%	29.8%	30.7%	31.3%
Hypertension	48.2%	50.1%	51.5%	53.2%	52.5%
Coronary heart disease	48.9%	50.7%	51.2%	52.8%	53.1%
Valve disease	18.8%	19.6%	18.8%	19.0%	19.8%
Baseline ECG					
Atrial fibrillation	41.5%	40.5%	40.3%	39.4%	38.0%
Left bundle branch block	12.0%	12.9%	12.7%	12.4%	11.6%
Previous myocardial infarction	1.7%	1.7%	1.9%	2.3%	2.5%
Baseline ECHO					
Diastolic dysfunction	0.7%	1.1%	1.1%	1.2%	1.1%
Left ventricular hypertrophy	1.0%	1.3%	1.1%	1.0%	0.8%
Valve disease	5.9%	6.6%	5.9%	5.6%	4.6%
Treated on Cardiology Ward	49.8%	54.2%	56.1%	56.1%	66.9%
Therapies					
ACE-I/ARB	78.6%	79.4%	79.9%	81.1%	81.8%
Beta-blocker	69.7%	70.7%	71.4%	73.2%	75.5%

ACEI/ARB = Angiotensin-converting enzyme inhibitor/Angiotensin-receptor blocker; ECG = electrocardiogram; ECHO = echocardiogram; HF = heart failure; NYHA = New York Heart Association.

* Rounded to nearest number from multiply imputed estimates.

hypertension, history of valve disease, atrial fibrillation, left bundle branch block, previous myocardial infarction, diastolic dysfunction, left ventricular hypertrophy and valve disease, prescription of ACE inhibitors/ARBs, aldosterone receptor antagonists, loop diuretics, thiazide diuretics, β blockers, digoxin, referral for HF specialist nurse follow-up, referral for palliative care follow-up, referral for geriatric follow-up, treatment on a cardiology ward, and dummy variables for year of admission (2007, 2008, 2009, 2010, 2011, 2012, and 2013). Second, propensity score matching was used to restrict any analysis to patients who were similarly likely to be referred to cardiology follow-up. Logistic regression was used to generate a propensity score for each patient being referred for cardiology follow-up. In total, 100 covariates were included in the logistic regression model: the same 34 baseline covariates as mentioned earlier and interaction terms between age, gender, and all covariates excluding age and gender. Patients referred for cardiology follow-up were then matched one-to-one without

replacement with subjects who were not referred for cardiology follow-up. The effectiveness of the matching process was gauged by examining the post-matching balance on covariates. Hierarchical logistic regression was performed on the matched sample, adjusting for all 34 covariates. Multiple imputation with chained equations was used to impute missing data; 5 imputations were generated. No covariate or outcome was missing at a rate exceeding 15%.

Study findings are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[5] No ethics approval was needed for this analysis; the National Heart Failure Audit was conducted with the approval of the NHS Information Center.

Results

Overall, 68,772 patients with HFREF discharged from 185 hospitals were included in the analyses. At the hospital

Table 3
Association between type of follow up and thirty day and one year mortality

	30-day Mortality		One Year Mortality	
	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Cardiology Follow Up vs. No Cardiology Follow Up				
Multivariable adjusted	0.66 (CI 0.61, 0.72)	p <0.001	0.74 (CI 0.70, 0.78)	p <0.001
Propensity score matched	0.66 (CI 0.58, 0.76)	p<0.001	0.74 (CI 0.67, 0.82)	p=0.002
Instrumental variable estimated	0.70 (CI 0.55, 0.89)	p=0.005	0.81 (CI 0.68, 0.95)	p=0.012

All models adjusted for 34 demographic, clinical and therapy variables. Age, gender, NYHA breathlessness, level of peripheral oedema, history of diabetes, history of hypertension, history of ischemic heart disease, history of valve disease, atrial fibrillation, left bundle branch block, evidence of myocardial infarction on baseline ECG, treatment in cardiology ward, treatment with aldosterone receptor antagonists, treatment with ACE inhibitors or ARB, treatment with beta blockers, treatment with digoxin, treatment with thiazide diuretics, treatment with loop diuretics, referral for specialist HF nurse follow up, referral for care of the elderly follow up, referral for palliative care follow up and baseline year of discharge. Propensity matched estimate is adjusted for the same variables, but matched on the interaction of all thirty variables with sex and age, in addition to the thirty covariates adjusted for.

level, rates of referral to cardiologists varied from 6% to 96%. The median odds ratio (OR) for referral to cardiologist was 2.3 (95% confidence interval [CI] 2.1 to 2.5), suggesting that, on average, the odds of a patient being referred for cardiologist follow-up after discharge differed ∼2.3 times from 1 randomly selected hospital to another one. Hospitals that were tertiary hospitals and that had greater numbers of consultant cardiologists had higher rates of referral to cardiology follow-up (Supplementary Table 1).

The predicted mortality for patients referred for cardiology follow-up was lower than those not referred for follow-up (26% vs 32%, Table 1). Patients referred for cardiology follow-up tended to be younger and more likely to be prescribed ACE inhibitors/angiotensin receptor blockers and β blockers at discharge (Table 1). Furthermore, patients referred for cardiology follow-up were more likely to be treated on a cardiology ward (70% of those referred for follow-up vs 38% of those not referred) (Table 1).

For the instrumental variable analysis, we first tested the validity of the instrument. The proportion of patients referred for cardiology follow-up varied significantly across regions, from 5% to 100% of patients. When regions were divided into fifths by proportion of patients referred for cardiology follow-up, patient characteristics were broadly similar (Table 2). Predicted 1-year mortality varied slightly across regions, ranging from 29% to 27% from the lowest to highest quintile of referral, although this difference was similar to previous analyses that used regional variation.[2]

When regional proportion of patients referred for cardiology follow-up was used as an instrument, referral for cardiology follow-up was significantly associated with lower 30-day (OR 0.70 95% CI 0.55 to 0.89) and reduced 1-year mortality (OR 0.81 95% CI 0.68 to 0.95, Table 3).

In hierarchical analysis, after adjustment, referral for cardiology follow-up was associated with a substantially lower risk of 30-day mortality (OR 0.66 95% CI 0.61 to 0.72) and 1-year mortality (OR 0.74 95% CI 0.70 to 0.78, Figure 1). After propensity score matching, 11,571 patients with HF referred for cardiology follow-up were matched to 11,571 patients with HF not referred for cardiology follow-up; 45,630 patients were excluded. Predicted 1-year mortality was very similar between patients who were and were not referred for cardiology follow-up (28% vs 28%, standardized
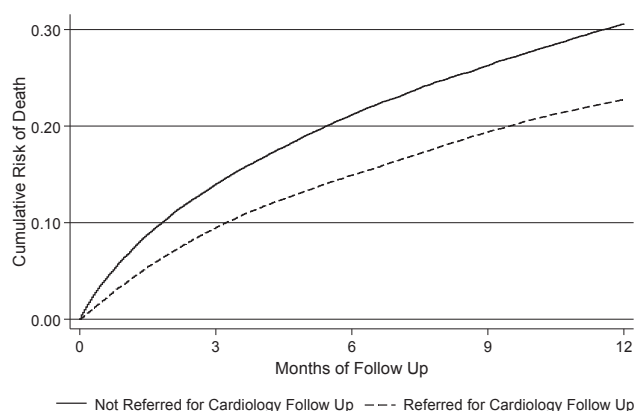

Figure 1. Risk of death adjusted (survival curves are plotted at the mean of each covariate using Cox regression) for 34 covariates and stratified by referral to cardiology follow-up.

difference of 0.8%), as was age, gender, breathlessness, and medical history (all standardized differences <2%, Table 1). After adjustment for 34 covariates on the matched sample, referral for cardiology follow-up was still associated with a substantially lower 30-day (OR 0.66 95% CI 0.58 to 0.76) and 1-year mortality (OR 0.74 95% CI 0.67 to 0.82). Estimates were similar when propensity score was also included in the model (data not shown).

Instrumental variable estimation of the association between referral for cardiology follow-up and 1-year mortality was not substantially different if early deaths were excluded (OR 0.84 95% CI 0.71 to 0.99, Table 4), although this did attenuate the effect on 30-day mortality (OR 0.84 95% CI 0.64 to 1.11), suggesting a very early impact of specialist care.

Discussion

We investigated the effect of the policy recommendation that patients with HFREF should have care by specialist cardiology services after discharge from hospital. Using instrumental variable method, which exploits natural random allocation of patients to a certain exposure variable (in this case referral for cardiology follow-up by small geographic regions), we show that referral to specialist

Table 4
Association between type of follow up and thirty day and one year mortality after exclusion of deaths in the first seven days

Cardiology Follow Up vs. No Cardiology Follow Up	30-day Mortality		One Year Mortality	
	Odds Ratio	p-value	Odds Ratio	p-value
Multivariable adjusted	0.70 (CI 0.63, 0.77)	p <0.001	0.75 (CI 0.71, 0.79)	p <0.001
Propensity score matched*	0.69 (CI 0.60, 0.81)	p <0.001	0.76 (CI 0.68, 0.85)	p <0.001
Instrumental variable estimated	0.84 (CI 0.64, 1.11)	p=0.226	0.84 (CI 0.71, 0.99)	0.034

All models adjusted for 34 demographic, clinical and therapy variables. age, gender, NYHA breathlessness, level of peripheral oedema, history of diabetes, history of hypertension, history of ischemic heart disease, history of valve disease, atrial fibrillation, left bundle blockers, evidence of myocardial infarction on baseline ecg, treatment in cardiology ward, treatment with aldosterone receptor antagonists, treatment with ACE inhibitors or ARB, treatment with beta blockers, treatment with digoxin, treatment with thiazide diuretics, treatment with loop diuretics, referral for specialist HF nurse follow up, referral for care of the elderly follow up, referral for palliative care follow up and baseline year of discharge. Propensity matched estimate is adjusted for the same variables, but matched on the interaction of all thirty variables with sex and age, in addition to the thirty covariates adjusted for. Instrumental variable estimate utilizes proportion of patients referred for cardiology follow up in 3360 regions.

* Non hierarchical logistic model used due to a lack of convergence with the hierarchical model. Standard errors instead adjusted for clustering at the hospital level.

cardiology services is strongly associated with lower risk of death after discharge. In this large national linked database, arrangement of a follow-up appointment after discharge with a cardiologist was associated with a 30% lower odds of death at 30 days after discharge (OR 0.70, 95% CI 0.55 to 0.89) and a 19% lower odds at 1 year after discharge (OR 0.81, 95% CI 0.68 to 0.95). These findings were robust to alternative statistical modeling techniques and assumptions.

To our knowledge, this is the first study to demonstrate that referral for cardiology follow-up soon after discharge with HF is associated with a substantial reduction in mortality. This has important implications for policy and practice to improve outcomes. As suggested in an earlier report, interventions to tackle the low referral rates after discharge could also contribute to reductions in between-hospital variation in quality of care.[6]

However, there are several potential limitations to our findings. First, we only examined the association of cardiology follow-up with mortality in HF with reduced ejection fraction as there are few recommended therapeutic interventions for HF with preserved ejection. Second, our analysis relied on retrospective registry data, which may contain recording errors of patients' diagnoses. Third, our instrumental variables analysis was not powered to examine the association of referral to cardiology follow-up with mortality in subgroups. Consequently the effect of cardiology follow-up on outcomes in certain subgroups of patients with HF, such as those who are New York Heart Association class I, may differ from the effect of cardiology follow-up in the overall HFREF population. Despite our rigorous design and analytical approach, we cannot entirely rule out that some of the association observed is because of unmeasured confounding factors. Policy interventions can be costly and a formal cost-effectiveness analysis might also be needed to guide decision makers about the costs and consequences of cardiology follow-up. In this context, future studies should also address the impact of the intervention on other important outcomes such as re-hospitalization.

Disclosures

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.amjcard.2016.10.021.

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