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Temporal Trends in Treatment and Outcomes for Advanced Heart Failure with Reduced Ejection Fraction from 1993-2010: Findings from a University Referral Center

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Abstract

Background—Randomized trials have demonstrated the efficacy of several new therapies for heart failure (HF) with reduced ejection fraction over the preceding two decades. This study investigates whether these therapeutic advances have translated into improvement in outcomes for patients with advanced HF referred to a heart transplant center.

Methods and Results—Patients with HF (n=2507) referred to a single university center were analyzed in three 6-year eras during which medical and device therapies were evolving: 1993-1998 (era 1), 1999-2004 (era 2), and 2005-2010 (era 3). Impaired hemodynamics and comorbidities were more frequent at time of referral in later eras, whereas other HF severity parameters where similar or improved. Successive eras had greater utilization of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, aldosterone antagonists, implantable cardioverter defibrillators, and cardiac resynchronization therapy, consistent with evolving evidence and guideline-recommendations over the study period. All-cause mortality and sudden death were significantly lower in era 2 and 3 compared to era 1. After multivariable risk adjustment, era 3 had significantly decreased 2- and 3-year all-cause mortality risk and significantly decreased 1- and 3-year sudden death risk compared to era 1. However, progressive HF death and the combined outcome of mortality / urgent transplant / ventricular assist device were modestly increased in the latter eras.

Conclusions—Over the past two decades, patients with advanced HF referred to and managed at a tertiary university referral center have benefited from advances in HF medications and devices, as evidenced by improvements in overall survival and sudden death risk.

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Keywords

heart failure; mortality; therapy

In the last two decades, randomized trials have identified several therapies that are efficacious in patients with heart failure (HF) and reduced ejection fraction (EF).[1] Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), beta blockers, and aldosterone antagonists have been shown to prolong survival in large randomized, placebo-controlled trials, forming the foundation of medical therapy for HF with reduced EF.[2-8] Major trials have also demonstrated the efficacy of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in improving outcomes of select patients with HF and reduced EF.[9-14]

Implementation of HF medical and device therapies associated with survival benefit in clinical trials is expected to improve survival in real-world HF populations. However, community- and population- based studies that consider temporal trends in outcomes have generally not examined long-term survival rates in advanced referral HF populations after the advent of modern medical and device therapies.[15-21] There are also other factors that may impact survival in advanced HF patients including differences in disease severity at time of referral, longer waiting times on heart transplant lists, and the increasing availability of ventricular assist devices (VADs). This study examines trends in treatment and outcomes in patients with advanced HF and reduced EF presenting to a university referral center for HF management and/or transplant/VAD evaluation between 1993 to 2010, a time period during which there were significant advances in medical and device therapies for HF.

Methods

Patients

The study was comprised of consecutive patients referred to the Ahmanson-UCLA Cardiomyopathy Center from 1993 to 2010. All patients were followed in a comprehensive management program for HF, as previously described.[22] Patients with left ventricular EF > 40% (n = 1881) were excluded from this study. The remaining patients (n = 2507) were considered in three six-year eras, 1993-1998 (era 1, n = 793), 1999-2004 (era 2, n = 879), and 2005-2010 (era 3, n = 835), a time period during which HF therapies were evolving, specifically with the introduction of beta-blockers, aldosterone antagonists, ICDs, and CRT. A prior publication from our center reported on temporal trends in clinical outcomes from 1986-1993.[23] Review of medical records was approved by the University of California-Los Angeles, Medical Institutional Review Board.

Baseline Data

Medications were recorded at time of referral and every visit thereafter. Diuretic doses were converted to furosemide equivalents. The formula used to convert other loop diuretics to furosemide equivalents was as follows: furosemide 80 mg = torsemide 40 mg = bumetanide 3 mg = ethacrynic acid 50 mg. Laboratory testing, echocardiography and cardiopulmonary exercise tests analyzed in this study all occurred within 3 months of initial referral. EF and dimensions were extracted from echocardiography reports; left ventricular end-diastolic dimension index (LVEDDI) was calculated as LVEDDI = left ventricular end-diastolic dimension (LVEDD)/body surface area (BSA). Past medical history was extracted from medical record review. Device therapy (CRT or ICD) in this study was considered “present” if the device had been placed before referral, or within 3 months of referral. Hemodynamic variables used in the analyses were the optimal values recorded after pulmonary artery

catheter-tailored medical therapy, as these measurements have been shown to best correlate with survival.[24]

End Points

The primary endpoint analyzed was all-cause mortality. Secondary endpoints analyzed were sudden death, progressive HF death, urgent transplant (UNOS status IA), VAD, and the combined endpoint of death, urgent transplant and VAD. All endpoints were assessed at one, two, and three years. Non-urgent transplants (status IB and II) were censored and considered as a nonfatal end of follow-up for the combined endpoint. Death was considered sudden if it was unexpected based on the patient's clinical status and if it occurred out of the hospital within 15 minutes of the onset of unexpected symptoms or during sleep, as defined previously.[23] Death during hospitalization for worsening congestive symptoms was considered a progressive HF death.

Statistical Analysis

Differences in baseline data between the three eras were analyzed using Pearson chi-square test, one-way analysis of variance (ANOVA), and non-parametric tests, as appropriate. Actuarial event curves for each era were calculated by the Kaplan Meier method, and differences in the curves were assessed by the log-rank statistic. Multivariable analyses adjusting for established predictors of HF outcomes, including age, gender, LVEF, NYHA class, body mass index (BMI), history of coronary artery disease (CAD), history of diabetes, history of hypertension, total cholesterol, serum sodium, serum blood urea nitrogen (BUN) and pulmonary capillary wedge pressure after optimization of therapy, were performed by Cox proportional hazards regression analysis to estimate adjusted hazard ratios and 95% confidence intervals (CIs). The Cox model retained all independent variables with $p<0.15$. Tests for trend were performed with the Cochran-Armitage test for actuarial and adjusted survival across the eras. Adjusted hazard curves were estimated graphically as 1-survival using the Cox model. To evaluate the severity of illness at time of referral, mortality risk scores and expected 1- and 3-year mortality rates for patients in each of the 3 eras were calculated using the Seattle HF Model (excluding adjustment for medications, other than loop diuretic doses, and devices), a previously developed model for predicting mortality in HF patients.[25] Probability values were 2-sided with $P<0.05$ considered statistically significant. Statistics were calculated using PASW Statistics, version 18.0 (IBM, Somers, NY).

Results

Patient characteristics for each era are shown in Table 1. Patients were 74% male with a mean age of 53 years. The left ventricular EF at time of referral was slightly lower in era 3 compared with the previous two eras ($p<0.001$). Diabetes and BMI were higher in later eras, and B-type natriuretic peptide (BNP) levels were higher in era 3 compared to era 2 ($p<0.001$). Lower LVEDDI and lower total cholesterol were also observed in later eras ($p<0.001$). The proportion of patients that were classified as New York Heart Association (NYHA) class IV functional class was lower in eras 2 and 3, with a concomitantly higher proportion of patients having NYHA class II and III disease ($p<0.001$). In terms of hemodynamic variables, heart rate was lower while right atrial pressure, systolic pulmonary artery pressure and pulmonary capillary wedge pressure were higher in later eras ($p<0.001$). The Seattle HF Risk Model score was highest in era 3 ($p=0.004$) (Table 1).

Management of HF

As expected, use of HF therapies varied strikingly across the eras (Table 2). The proportion of patients receiving aldosterone antagonists, beta blockers, ICD, and CRT was substantially

higher in the later eras (p<0.001). ACEI/ARB use remained at a high level in all eras with a small decrease seen in era 3 compared to era 2. Nitrates, hydralazine and loop diuretics were used by fewer patients in later eras. The proportion of patients receiving anticoagulation was unchanged over the study period.

Temporal Trends in Outcomes

The primary outcome of all-cause mortality was significantly lower at one and three years in era 2 and 3 (Table 3 and Figure 1). Sudden death was lower in later eras (Table 3 and Figure 2). However, mortality from progressive HF death was higher in era 3 compared to era 1 (Table 3 and Figure 2). The combined endpoint of all-cause mortality, urgent transplant, or VAD was lower in era 2 but was higher in era 3 (Figure 1). This is largely accounted for by the higher rate of urgent heart transplantation (UNOS status 1a) and VAD implantation in the last era (Table 3). There were lower rates of non-urgent heart transplantation in era 2 and 3 (Table 3). The median times from referral to urgent transplantation were similar in all 3 eras (2.1, 2.4, and 2.1 months, p=0.929). The time from referral to non-urgent transplantation also did not statistically differ in the 3 eras (8.5, 11.9, and 7.8 months, p=0.091).

Risk-Adjusted Analysis of Outcomes

After adjusting for known predictors of HF mortality, era 3 was independently associated with decreased risk of all-cause mortality compared to era 1 at two and three years, with a borderline p value at one-year follow-up (Table 4 and Figure 1). Compared to era 1, era 3 was associated with a 42% lower adjusted relative risk of mortality during 3-year follow-up (hazard ratio [HR] 0.58, 95% confidence intervals [CI] 0.40-0.85). Era 3 was independently associated with decreased risk of sudden death compared to era 1 at one and three years, with a borderline p value (p=0.057) for decreased risk at two years (Table 4 and Figure 2). In contrast, after multivariable adjustment, latter eras were not independently associated with lower or higher risk of progressive HF death with the exception of a higher risk seen for era 2 at one year. After multivariable analysis era 2 had a higher risk of the combined endpoint of mortality, urgent transplant, or VAD (Table 4). Unadjusted and risk-adjusted hazard curves for the outcome of all-cause mortality and the composite of mortality, urgent transplant, or VAD are shown in Figure 1.

Discussion

The major findings of this study are that over successive time periods from 1993 to 2010, there has been a marked increase in the use of evidence-based therapies in advanced HF patients with reduced EF referred to a tertiary university HF center, with a corresponding improvement in overall survival in this patient population. Sudden cardiac death was also significantly lower in later eras. Concomitant with a substantial decrease in sudden death was a modest increase in progressive HF death, urgent transplants, and VADs. After risk adjustment, there was a lower risk of all-cause mortality and sudden death for patients treated in the 2005-2010 time frame compared to 1993 to 1998. Although rates of progressive HF death were high in the later eras, this is not surprising given that sudden deaths were significantly lower in later eras and likely reflects a shifting mode of death. These findings confirm the successful translation of evidence-based care in treatment of advanced referral patients with HF and reduced EF from clinical trials to patients in real-world clinical practice.

The severity of HF disease state at time of referral to our university center seems to be worsened in later eras in our HF population by some, but not other, measures. Over the past two decades as documented in this study, patients in the later eras had modest but

significantly worse hemodynamic status, as indicated by higher pulmonary artery pressure, higher pulmonary capillary wedge pressure, and lower cardiac index, measured after medical optimization. Furthermore, Seattle HF Model risk score and predicted mortality were highest in the last era. However, other individual parameters including NYHA class, peak VO2, left ventricular end-diastolic dimension, systolic blood pressure, and heart rate did not indicate increased disease state severity at time of referral. A prior publication reporting on temporal trends in clinical outcomes at our center from an earlier time period 1986-1993 found that patients in the different time periods had similar hemodynamic variables after tailored therapy.[23] This study cohort also has increased comorbidities in later eras as indicated by higher rates of diabetes and atrial fibrillation, lower hemoglobin levels, and higher creatinine levels in the later eras; this increase in comorbidities over time is congruent with findings from other studies of HF populations. In an epidemiological study of HF in Western Australia, Teng et al found that prevalence of ischemic heart disease fell while prevalence of hypertension, diabetes, atrial fibrillation and renal failure rose from 1990-2003.[19] One study of Medicare beneficiaries hospitalized for HF found increased prevalence of hypertension, diabetes, anemia and pneumonia from 1993-2006, while another study described increased prevalence of hypertension and renal failure;[16, 18] similar trends in prevalence of comorbid conditions are noted in our population.

The successful translation of life-prolonging medications and devices for HF and reduced EF, from clinical trial to real-world populations, seen in this study is echoed in other publications of HF trends over the last decades. Jhund et al showed significant increases in prescribing rates of ACEI, beta blockers and spironolactone from 1986-2003 for patients with HF in Scotland.[26] More recently, Cubbon et al found increased usage of medications, ICD and CRT in a 2006-2009 cohort compared to a 1993-1995 cohort of patients with stable HF in the United Kingdom.[27] Our study extends this finding to a population of advanced HF patients referred to a tertiary center for heart transplant or VAD evaluation, with higher rates of beta blocker and aldosterone antagonist use as well as device implantation seen in the later eras of treatment.

Community, population and cohort studies have shown improved survival in HF populations over the past two decades, similar to the trends observed in the present analysis. An older study from a community cohort in Olmstead County, Minnesota showed reduced mortality in men after onset of HF from 26% in 1985-1990 to 21% in 1996-2000.[21] Several additional studies have shown general improvement in survival after hospitalization for HF;[16, 18, 19, 26, 28] US Medicare beneficiaries had modest increases in thirty-day and one-year survival after hospitalization for HF, with the number of hospitalizations falling from 1998 to 2008.[16, 18] Jhund et al also showed that mortality after hospitalization for HF fell in Scotland from 1995 to 2003, coinciding with the increase in prescribing rates for ACEIs, beta blockers and spironolactone during this time period.[26] A larger 38% decrease in all-cause mortality at one year between the 1993 –1995 cohort and the 2006 – 2009 cohort of stable HF patients in the United Kingdom was demonstrated by Cubbon et al.[27] Singh et al found that the risk of dying while listed for heart transplant or becoming too sick for transplant has decreased in the US after the implementation of a new sharing algorithm for these organs in 2006.[29] Our study of an advanced HF population referred to a tertiary center for heart transplant or VAD evaluation demonstrates a 13% and 42% lower risk of all-cause mortality at three years for eras 2 and 3 respectively (p trend = 0.006) compared to era 1 among patients with reduced EF treated at our center after adjustment for multiple known predictors of HF mortality.

Outcomes in patients with advanced HF over the past 20 years may also have been influenced by differences in waiting times for transplantation, rates of transplantation, and use of VADs in the three eras. In our cohort, waiting times for urgent and non-urgent

transplantation did not significantly change during the 3 eras, suggesting differences in transplantation waiting times are unlikely to account for the improved survival in latter eras. There were, however, higher rates of urgent transplantation in era 3 which may contribute to the lower mortality rates observed. However, there was also a decrease in non-urgent transplants, which may in part account for the higher rate of urgent transplants. Lastly, the use of VADs remained low across the eras, even in era 3, suggesting access to this new technology did not significantly affect the differences in outcomes.

Study Limitations

We acknowledge some limitations to our study. This study is observational and evaluates a cohort of patients with advanced HF referred to a single university center. As it was observational in nature, we cannot establish causality between increased use of evidence-based therapies and decreased mortality observed over the study period. Also, we cannot exclude that other factors, such as increased understanding of and compliance with lifestyle modifications and HF disease management, may be reflected in our results. Our findings reflect a single center referral experience and findings may not be able to be generalized to other settings. While we adjusted for multiple variables of established prognostic significance in patients with advanced HF, there are other established markers that were not included. The assessment of NYHA class potentially shifted over time with differing clinician experience expectations; in era 1 the majority of the patients (58%) were classified as NYHA IV while in era 2 and 3 only 29% of patients were classified as NYHA IV, even though other measures of HF severity were similar or worse. There may be residual measured and unmeasured confounding variables that account for some or all of these findings. There are also well-recognized limitations in distinguishing between different modes of death in patients with HF so the findings regarding different time trends in mode of death should be interpreted with these limitations in mind. Lastly, the time period of our study predates a more recent increase in VAD usage, and so we cannot determine how higher rates of VAD usage may affect long term HF outcomes.

Conclusions

In a cohort of patients with advanced HF and reduced EF referred to and managed at a tertiary university referral center from 1993 to 2010, there has been successive application of evidence-based, guideline-recommended therapies, coincident with improvement in overall survival and lower sudden death risk over time. Increased rates of HF deaths, transplants, and VADs in the later eras were seen, and are potentially attributable to different risk profiles at time of referral and substantial reductions in sudden death in later eras;. Lastly, despite improvement in survival over the past two decades, the all-cause mortality rate for advanced HF with reduced EF at three years remains at approximately 30%, indicating the need to continue seeking new treatment options and management strategies for this prevalent problem with significant relevance to public health.

Clinical Perspective

Heart failure is a major public health problem affecting close to 6 million men and women in the United States. In the last 20 years, randomized trials have demonstrated the efficacy of several new therapies for heart failure with reduced ejection fraction and changed treatment paradigms. However, the impact that this has had on real-world patient outcomes is still largely unknown. Using data from 2507 patients with heart failure and reduced ejection fraction referred to and followed at a single university tertiary referral center, this study examines trends in clinical characteristics, management, and outcomes across therapeutic eras in the last two decades. Comorbidities and impaired hemodynamics were more frequent

at referral in the later eras, whereas other parameters of heart failure severity were similar to the first era or improved. Management of heart failure with use of beta-blockers, aldosterone antagonists, implantable cardioverter defibrillators and cardiac resynchronization therapy increased significantly, consistent with evolving evidence and guideline-recommendations during the study period. At one-, two- and three-year follow-up, all-cause mortality and sudden death were significantly lower in the later eras of treatment, and the most recent era was independently associated with a decreased risk of all-cause mortality and sudden death in multivariable analysis. The waiting time to heart transplantation did not change significantly in the study period. Taken together, this study demonstrates patients with advanced heart failure have benefited from recent advances in evidence-based, guideline-recommended heart failure therapies, with improvement in survival and lower sudden death risk over time.

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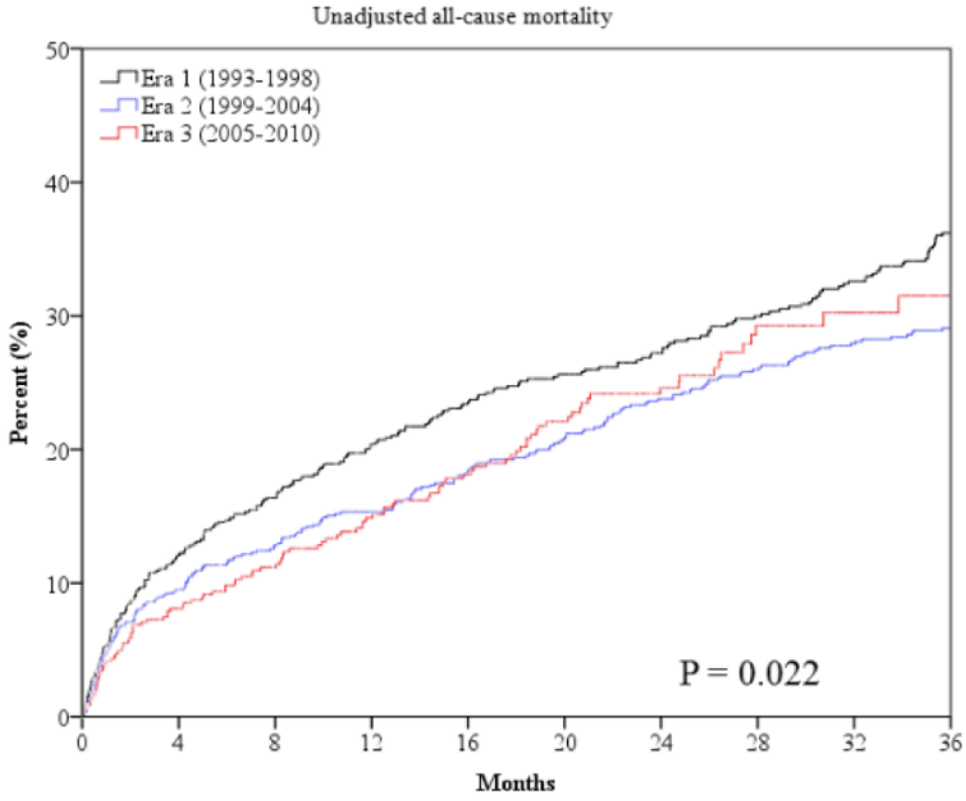

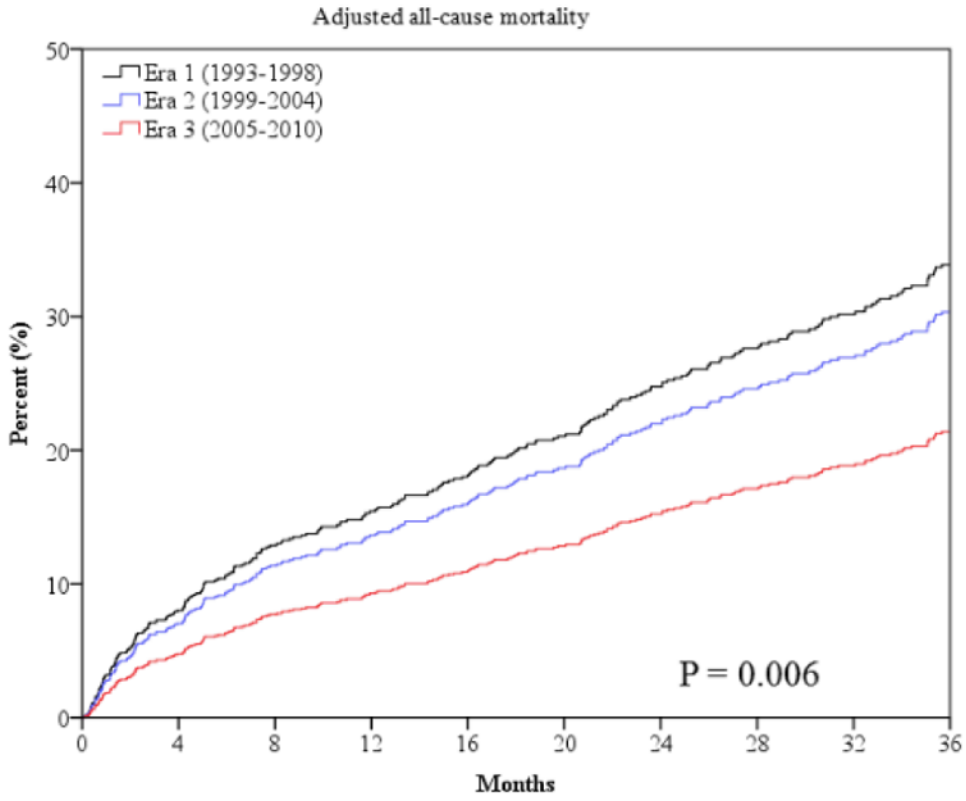

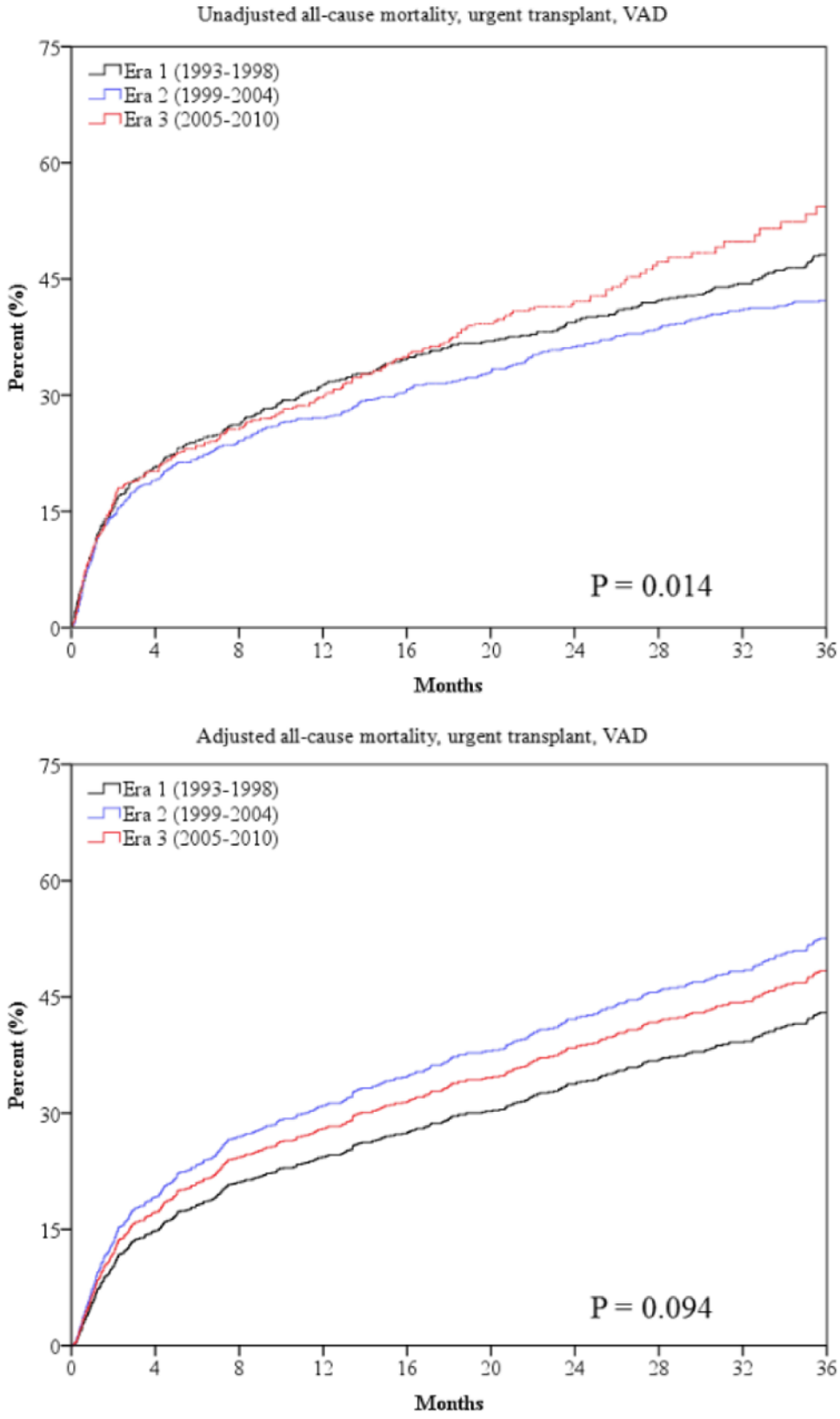

Figure 1.

Unadjusted and risk-adjusted survival curves for the outcome of all-cause mortality (panels a and b) and all-cause mortality, urgent transplant and VAD (panels c and d).
Risk adjusted survival curves are adjusted for patients' age, gender, LVEF, NYHA class, body mass index, history of CAD, history of diabetes, history of hypertension, total cholesterol, serum sodium, serum BUN and pulmonary capillary wedge pressure after optimization of therapy. P values for unadjusted curves (panels a and c) are derived from log-rank statistic. P values for adjusted curves (panels b and d) are derived from Cochran-Armitage trend test.

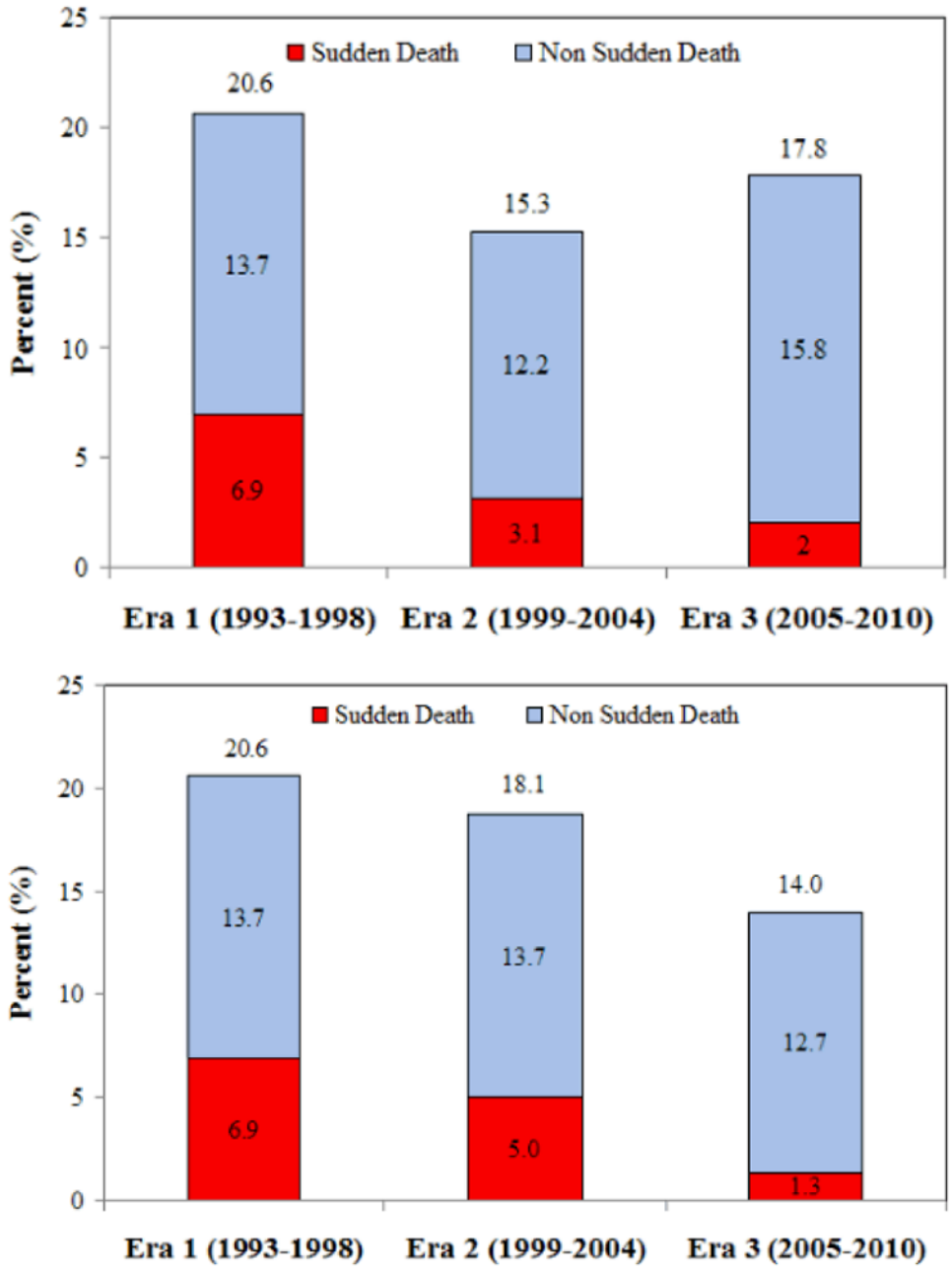

Figure 2.

Sudden death, non sudden death, and total mortality at one year in the three eras, (a) unadjusted and (b) adjusted rates.

See figure 1 legend for adjustment variables.

Table 1
Patient Characteristics in the Successive Treatment Eras

	Era 1 1993-1998 (n=793)	Era 2 1999-2004 (n=879)	Era 3 2005-2010 (n=835)	P value*
N	793 (31.6%)	879 (35.1%)	835 (33.3%)	
Age (yr)	53.5±12.2	52.8±13.4	53.9±12.9	0.214
Male (%)	75.2%	74.1%	73.1%	0.650
Ischemic etiology of HF (%)	44.8%	43.6%	40.5%	0.201
NYHA class (%)				<0.001
I	0.5%	4.1%	5.9%	
II	8.6%	22.6%	21.4%	
III	32.5%	44.0%	43.9%	
IV	58.4%	29.3%	28.7%	
LVEF (%)	23.5±6.62	24.1±7.32	22.3±7.74	<0.001
Body Mass Index	26.1±5.37	27.1±5.56	27.6±5.96	<0.001
Diabetes (%)	25.9%	25.3%	30.5%	0.034
Hypertension (%)	42.1%	38.4%	40.9%	0.275
Smokers (past or present) (%)	65.7%	50.0%	51.5%	<0.001
LVEDD (mm)	70.0±10.4	66.6±11.0	65.4±12.1	<0.001
LVEDDI (mm/m^2)	36.8±6.45	34.3±6.37	33.5±6.90	<0.001
Peak VO2 (ml/kg/min)	14.2±4.73	13.5±4.98	13.9±6.24	0.149
Severe MR (%)	29.1%	15.3%	15.4%	<0.001
Severe TR (%)	15.8%	6.7%	9.7%	<0.001
Atrial fibrillation (%)	18.5%	23.4%	37.9%	<0.001
Time from first HF symptoms to referral (months)‡	39 (8, 88)	17 (4, 57)	28 (6, 80)	<0.001
Laboratories				
Sodium (mmol/L)	136±4.71	136±4.64	136±6.52	0.703
Creatinine (mg/dL)	1.40±0.760	1.51±1.37	1.55±1.66	0.057
Blood urea nitrogen (mg/dL)	27.4±17.1	28.5±20.1	30.0±20.7	0.037
Hemoglobin (g/dL)	13.4±1.93	13.1±1.93	13.1±2.68	0.003
Total cholesterol (mg/dL)	177±55.6	166±55.3	147±50.6	<0.001
HDL (mg/dL)	35.4±14.5	38.7±15.1	37.6±17.8	<0.001
LDL (mg/dL)	112±42.8	97.4±39.3	83.8±36.8	<0.001
Triglycerides (mg/dL)‡	101 (67, 170)	114 (74, 183)	107 (74, 165)	0.014
B-type natriuretic peptide (pg/mL)‡		472 (154, 1150)	661 (253, 1540)	<0.001
Hemodynamics†				
Heart Rate (beats/min)	86±17	81±16	82±16	<0.001
Systolic Blood Pressure (mm Hg)	102±17	109±20	104±18	<0.001
Diastolic Blood Pressure (mm Hg)	56±12	65±14	65±13	<0.001
Right Atrial Pressure (mm Hg)	7±4	9±6	9±5	<0.001
Systolic Pulmonary Artery Pressure (mm Hg)	38±11	40±13	42±13	<0.001

	Era 1 1993-1998 (n=793)	Era 2 1999-2004 (n=879)	Era 3 2005-2010 (n=835)	P value*
Diastolic Pulmonary Artery Pressure (mm Hg)	18±6	20±7	21±8	<0.001
Pulmonary Capillary Wedge Pressure (mm Hg)	15±6	17±7	18±7	<0.001
Cardiac Output (L/min)	4.7±1.1	4.5±2.2	4.4±2.7	0.010
Cardiac Index (L/mm^2)	2.5±0.56	2.3±0.97	2.3±1.6	0.001
Systemic Vascular Resistance (dyn*s/cm^5)	1110±290	1300±425	1320±496	<0.001
Clinical Risk Score				
Seattle HF Model Score	2.17±0.75	2.07±0.80	2.28±1.09	0.004
Expected 1-year mortality	29.9%	27.5%	32.7%	
Expected 3-year mortality	65.5%	61.8%	69.5%	

NYHA, New York Heart Association; LVEDD, left ventricular end-diastolic dimension; LVEDDI, left ventricular end-diastolic dimension index; VO_2, oxygen consumption; MR, mitral regurgitation; TR, tricuspid regurgitation; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Categorical variables are presented as percentage of patients, and continuous variables are presented as mean ± standard deviation.

*P values reflect Pearson chi-square test for categorical variables, one-way analysis of variance for normally distributed continuous variables and

‡non-parametric tests for non-normally distributed continuous variables.

†After optimization of medical therapy.

Table 2
Heart Failure Therapies in the Successive Treatment Eras

	Era 1 1993-1998 (n=793)	Era 2 1999-2004 (n=879)	Era 3 2005-2010 (n=835)	P value*
Drugs				
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker, %	86.5	89.5	78.8	<0.001
Beta blocker, %	15.5	75.9	87.1	<0.001
Aldosterone antagonist, %	6.5	49.0	57.9	<0.001
Loop diuretic, %	87.9	83.5	82.0	0.004
Mean dose of loop diuretic (mg) (furosemide equivalent)	119	89	88	<0.001
Coumadin, %	43.7	41.9	41.4	0.611
Hydralazine, %	13.8	5.9	7.4	<0.001
Metolazone, %	9.0	9.8	12.8	0.067
Nitrate, %	62.1	23.7	19.7	<0.001
Statin, %	22.1	50.2	49.2	<0.001
Device therapies				
Cardiac resynchronization therapy, %†	0.0	10.2	39.2	<0.001
Implantable cardioverter defibrillator, %†	11.1	35.2	65.7	<0.001

Therapy usage is presented as percentage of patients.

*P values reflect Pearson chi-square test.

†Percentages reflect patients' year of referral.

Table 3

Event Rates During the Successive Treatment Eras (Unadjusted)

	Era 1 1993-1998 (n=793)	Era 2 1999-2004 (n=879)	Era 3* 2005-2010 (n=835)	P value†	P trend‡
All-cause mortality					
1 yr	20.6%	15.3%	17.8%	0.042	0.114
2 yr	27.9%	23.8%	25.5%	0.121	0.109
3 yr	36.4%	29.4%	31.5%	0.022	0.029
Sudden death					
1 yr	6.9%	3.1%	2.0%	<0.001	<0.001
2 yr	8.1%	5.1%	4.7%	0.002	0.001
3 yr	10.1%	6.4%	4.6%	0.001	<0.001
Progressive HF death					
1 yr	7.1%	7.0%	12.6%	0.002	0.002
2 yr	9.6%	9.4%	16.9%	0.004	0.006
3 yr	11.6%	11.3%	19.9%	0.004	0.007
Urgent transplant or VAD					
1 yr	13.9%	14.0%	19.9%	0.002	0.002
2 yr	16.7%	16.5%	23.9%	0.002	0.003
3 yr	18.9%	18.5%	33.4%	<0.001	0.001
Urgent transplant					
1 yr	13.9%	14.0%	18.7%	0.020	0.014
2 yr	16.7%	16.5%	23.7%	0.002	0.003
3 yr	18.9%	18.5%	33.4%	<0.001	0.001
VAD					
1 yr	0%	0%	1.4%	<0.001	0.038
2 yr	0%	0%	0.2%	0.291	0.498
3 yr	0%	0%	0%	N/A	N/A
Non-urgent transplant					
1 yr	11.2%	6.7%	8.1%	0.015	0.039
2 yr	16.7%	11.7%	14.1%	0.029	0.053
3 yr	19.4%	14.8%	15.9%	0.065	0.097

	Era 1 1993-1998 (n=793)	Era 2 1999-2004 (n=879)	Era 3* 2005-2010 (n=835)	P value†	P trend‡
Mortality, urgent transplant or VAD					
1 yr	31.6%	27.2%	34.2%	0.018	0.311
2 yr	40.0%	36.4%	45.3%	0.059	0.426
3 yr	48.5%	42.5%	53.4%	0.014	0.669

† P values reflect the log rank (Mantel-Cox) test.

* 2005-2009 and 2005-2008 for 2 and 3 year analyses, respectively.

‡ P value for trend from the Cochran-Armitage test.

Table 4

Risk-Adjusted All-Cause Mortality, Cause Specific Mortality, and Composite Hazard Ratios in Successive Treatment Eras

	Era 1 1993-1998	Era 2 1999-2004	Era 3† 2005-2010	Era 1 1993-1998	Era 2 1999-2004	Era 3† 2005-2010	P trend‡
	Unadjusted hazard ratios			Adjusted hazard ratios*			
1-year HR (95% CI)							
All-cause mortality	1.00	0.74 (0.58-0.94) p=0.013	0.83 (0.65-1.06) p=0.141	1.00	0.91 (0.63-1.32) p=0.618	0.68 (0.45-1.04) p=0.072	0.080
Sudden death	1.00	0.45 (0.27-0.74) p=0.002	0.24 (0.12-0.48) p<0.001	1.00	0.73 (0.36-1.48) p=0.384	0.19 (0.05-0.64) p=0.007	0.006
Progressive HF death	1.00	1.01 (0.69-1.48) p=0.969	1.70 (1.19-2.42) p=0.004	1.00	1.95 (1.07-3.56) p=0.029	1.65 (0.88-3.11) p=0.122	0.124
Mortality, urgent transplant or VAD	1.00	0.85 (0.71-1.02) p=0.078	1.10 (0.92-1.31) p=0.305	1.00	1.61 (1.25-2.07) p<0.001	1.37 (1.04-1.80) p=0.023	0.013
2 year HR (95% CI)							
All-cause mortality	1.00	0.82 (0.67-1.00) p=0.053	0.85 (0.67-1.06) p=0.144	1.00	0.95 (0.69-1.30) p=0.738	0.67 (0.46-0.97) p=0.035	0.047
Sudden death	1.00	0.57 (0.37-0.88) p=0.012	0.42 (0.24-0.72) p=0.002	1.00	0.97 (0.53-1.77) p=0.909	0.43 (0.18-1.03) p=0.057	0.085
Progressive HF death	1.00	0.99 (0.71-1.40) p=0.972	1.59 (1.14-2.22) p=0.006	1.00	1.58 (0.95-2.64) p=0.081	1.27 (0.72-2.26) p=0.410	0.354
Mortality, urgent transplant or VAD	1.00	0.89 (0.76-1.04) p=0.141	1.08 (0.92-1.28) p=0.359	1.00	1.48 (1.18-1.85) p=0.001	1.28 (0.99-1.64) p=0.057	0.027
3-year HR (95% CI)							
All-cause mortality	1.00	0.78 (0.65-0.94) p=0.008	0.82 (0.65-1.02) p=0.075	1.00	0.87 (0.66-1.16) p=0.355	0.58 (0.40-0.85) p=0.005	0.006
Sudden death	1.00	0.58 (0.39-0.86) p=0.007	0.41 (0.23-0.72) p=0.002	1.00	0.95 (0.54-1.65) p=0.842	0.35 (0.14-0.87) p=0.024	0.042
Progressive HF death	1.00	0.99 (0.72-1.37) p=0.973	1.62 (1.16-2.26) p=0.005	1.00	1.34 (0.83-2.16) p=0.232	1.02 (0.57-1.90) p=0.955	0.822
Mortality, urgent transplant or VAD	1.00	0.85 (0.74-0.99) p=0.033	1.08 (0.91-1.27) p=0.391	1.00	1.33 (1.08-1.64) p=0.008	1.18 (0.92-1.51) p=0.197	0.094

P values reflect the likelihood ratio test by the Cox model.

*Multivariate analysis is adjusted for patients' age, gender, LVEF, NYHA class, body mass index, history of CAD, history of diabetes, history of hypertension, total cholesterol, serum sodium, serum BUN and pulmonary capillary wedge pressure after optimization of therapy.

†2005-2009 and 2005-2008 for 2 and 3 year analyses, respectively.

‡P value for trend from Cochran-Armitage test for adjusted models.