

Incremental Value of Implantable Cardiac Device Diagnostic Variables Over Clinical Parameters to Predict Mortality in Patients With Mild to Moderate Heart Failure

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Background—Heart failure remains a leading cause of morbidity and mortality. Clinical prediction models provide suboptimal estimates of mortality in this population. We sought to determine the incremental value of implantable device diagnostics over clinical prediction models for mortality.

Methods and Results—RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial) patients with implanted devices capable of device diagnostic monitoring were included, and demographic and clinical parameters were used to compute Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) heart failure risk scores. Patients were classified according to MAGGIC score into low (0–16), intermediate (17–24), or high (>24) risk groups. Mortality was evaluated from 6 months postimplant in accordance with the RAFT protocol. In a subset of 1036 patients, multivariable analysis revealed that intermediate and high MAGGIC scores, fluid index, atrial fibrillation, and low activity flags were independent predictors of mortality. A device-integrated diagnostic parameter that included a fluid index flag and either a positive atrial fibrillation flag or a positive activity flag was able to significantly differentiate higher from lower risk for mortality in the intermediate MAGGIC cohort. The effect was more pronounced in the high-risk MAGGIC cohort, in which device-integrated diagnostic-positive patients had a shorter time to death than those who were device-integrated diagnostic negative.

Conclusions—Device diagnostics using a combination of fluid index trends, atrial fibrillation burden, and patient activity provide significant incremental prognostic value over clinical heart failure prediction scores in higher-risk patients. This suggests that combining clinical and device diagnostic parameters may lead to models with better predictive power. Whether this risk is modifiable with early medical intervention would warrant further studies.

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Key Words: device diagnostics • heart failure • implantable cardioverter-defibrillator • model • mortality • prognostic factor

Heart failure (HF) remains a leading cause of morbidity and mortality, affecting 23 million people worldwide. In contrast to other forms of cardiovascular conditions, its prevalence and mortality rates continue to increase. Almost 50% of patients with HF will die within 5 years of diagnosis,

and up to 40% of patients die within 1 year of hospitalization.^{1,2} A reliable means of identifying vulnerable patients at higher risk may help identify those in need of closer monitoring and more immediate medical attention. Several clinical prediction models have been developed to help stratify risk in patients with HF. Unfortunately, many of them have poor to modest discrimination and inconsistent performance in the greater HF population. This may partly be attributed to the evolution of HF management over time and the fact that many of these models were derived from patient cohorts recruited >20 years ago.^{3,4} Among the more contemporary models is the recently derived Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) HF prediction score.⁴ It is based on the largest available database and, and unlike many of its predecessors, incorporates both preserved and reduced ejection fraction. Although it is among the most comprehensive and generalizable in the

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Clinical Perspective

What Is New?

- Heart failure (HF) clinical prediction models provide suboptimal estimates of mortality risk when used in isolation.
- Many patients with HF have therapeutic implantable cardiac devices that can provide a wealth of diagnostic data.
- In this substudy of RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial), we showed that device diagnostic data, including abnormal fluid index, low activity levels, and atrial fibrillation, provided incremental prognostic value to a validated clinical HF prediction model.

What Are the Clinical Implications?

- In patients with implantable electronic cardiac devices, the combination of clinical prediction models and device diagnostic parameters may help improve risk stratification in the high-risk population with HF.
- This may facilitate the identification and more timely intervention on patients with HF who are at highest risk of death.

available literature, the model calibration is not perfect in isolation.^{4,5}

Implantable cardiac devices with diagnostic features in patients with HF have provided an alternative means of monitoring and evaluating these patients. Diagnostic physiologic parameters collected by implantable devices (eg, night heart rate, activity, atrial fibrillation [AF] burden, and intrathoracic impedance) have been shown to correlate with adverse clinical events, such as HF hospitalizations.^{6–11} A model combining various device diagnostic parameters further improves on the predictive power of individual device parameters,^{12,13} with some evidence correlating these measurements with the risk of death.^{14,15} Although clinical parameters and device diagnostics have been separately investigated for risk prediction models, the combined clinical utility of clinical and device diagnostic parameters has yet to be studied. In this study, we sought to determine the incremental value of implantable device diagnostics over a well-validated clinical prediction model of mortality risk in patients with mild to moderate systolic HF.

Methods

Study Population

A retrospective analysis of device and clinical data was performed on the RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial) patient cohort. RAFT was a multicenter randomized controlled trial comparing implantable

cardioverter-defibrillator (ICD) versus cardiac resynchronization therapy–ICD in patients with mild to moderate HF (New York Heart Association class II–III), left ventricular systolic dysfunction (ejection fraction $\leq 30\%$), and wide QRS (≥ 120 ms). The rationale, design, and outcomes of this study have been published previously^{16,17} and complied with the Declaration of Helsinki. This study was also approved by an institutional review committee, and all subjects gave written informed consent to participate in the study. The data that support the findings of this study are available from the corresponding author on reasonable request.

To summarize, in RAFT, a total of 1798 patients were enrolled at 34 centers from January 2003 through February 2009. The average age was 66 ± 9.4 years, 82.9% were men, 67.0% had ischemic heart disease, and 80.0% had New York Heart Association class II functional capacity with an average left ventricular ejection fraction of $22.6 \pm 5.3\%$. Over a mean follow-up duration of 40 months, a total of 422 patients (23.5%) died; 292 deaths (16.2%) were attributable to cardiovascular causes.

Of the 1798 study participants, those implanted with a device capable of device diagnostic monitoring with >180 days of follow-up were included in this analysis. Baseline demographic and laboratory data required to calculate the MAGGIC HF prediction score were collected for each patient (Figure 1). Patients were then classified according to their MAGGIC score into low (0–16), intermediate (17–24), or high (>24) risk groups. Mortality was evaluated from 6 months postimplant forward and determined in accordance with the RAFT protocol.¹⁶

Device Diagnostic Parameters

The devices included in the analysis had the following 6 diagnostic parameters available: activity, AF burden, night heart rate, ICD shock, percentage biventricular pacing, and fluid index (FI). These parameters were associated with a defined “flag” that is triggered when a parameter exceeds a threshold value. A parameter is flagged when it reaches an abnormal range that is associated with worsening status of the patient. The flags for these parameters are as follows: activity flag defined as a mean activity <60 min/d for ≥ 1 week detected by the device’s piezoelectric sensor, AF flag defined as ≥ 6 hours of AF on at least 1 day, ventricular rate flag defined as ventricular rate >100 beats per minute and AF ≥ 6 hours for ≥ 1 day, night heart rate flag defined as any 7 consecutive days with average night heart rate (midnight to 4 AM) >85 beats per minute, shock flag defined as any ICD shock, ventricular pace flag defined as a mean percentage biventricular pacing $<90\%$ for patients with cardiac resynchronization therapy defibrillator, and FI flag defined as >14 days above intrathoracic impedance threshold

Risk Factor	Addition to Risk Score							Risk Score
Ejection Fraction (%)	<20 +7	20-24 +6	25-29 +5	30-34 +3	35-39 +2	>40 0		
Extra for age (yrs)	>55 0	56-59 +1	60-64 +2	65-69 +4	70-74 +6	75-79 +8	>80 +10	
EF<30	0	+1	+2	+4	+6	+8	+10	
EF 30 – 39	0	+2	+4	+6	+8	+10	+13	
EF>40	0	+3	+5	+7	+9	+12	+15	
Extra for SBP (mmHg)	<110 +5	110-119 +4	120-129 +3	130-139 +2	140-149 +1	>150 0		
	+3	+4	+1	+1	0	0		
	+2	+2	+1	0	0	0		
	+1							
BMI (kg/m²)	<15 +6	15-19 +5	20-24 +3	25-29 +2	>30 0			
Creatinine (µmol/L)	<90 0	90-109 +1	110-129 +2	130-149 +3	150-169 +4	170-209 +5	210-249 +6	>250 +8
NYHA Class	1 0	2 +2	3 +6	4 +8				
Male				+1				
Current smoker				+1				
Diabetic				+3				
COPD				+2				
First diagnosis of HF in past 18 months				+2				
Not on beta-blocker				+3				
Not on ACEI/ARB				+1				

Figure 1. Meta-Analysis Global Group in Chronic Heart Failure score. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; HF, heart failure; NYHA, New York Heart Association; SBP, systolic blood pressure. Reprinted from Pocock et al⁴ with permission. Copyright ©2013, Oxford University Press.

determined from the impedance measurement of the initial 6 months after device implant. FI (Optivol; Medtronic Inc, MN) is a previously described and validated parameter¹⁸ derived from intrathoracic impedance measurements taken from the right ventricular coil to the pulse generator that were extracted from routine device interrogations.

Statistical Analysis

Device diagnostic data from the first 6 months of follow-up were used to categorize the subjects as positive or negative of all 6 diagnostic parameters. Mortality was evaluated using follow-up data from RAFT. Data collected at baseline and follow-up were used in the calculation of the MAGGIC score. Ejection fraction, age, height, sex, current smoker, diabetes mellitus, and diagnosis of chronic obstructive lung disease

were evaluated at baseline. The most recent value available during the first 6 months of follow-up was used for systolic blood pressure, weight, creatinine, New York Heart Association class, and medication status. All the subjects had a first diagnosis of HF >18 months. Height measurements required for calculation of the body mass index were missing for 130 subjects. These missing data were imputed using the median height by sex from RAFT to calculate body mass index.

Univariable and multivariable hazard ratios (HRs) along with the 95% CIs were estimated using a Cox proportional hazards model. A test of proportionality was performed for the Cox model by adding time-dependent covariates to the model. The time-dependent covariates were generated by creating interactions of the predictor variables and a function of survival time. Activity flag, AF flag, ventricular rate flag, night heart rate flag, shock flag, ventricular pace flag, FI flag, and

Table 1. Baseline Characteristics

Characteristics	All (n=1036)	CRT-D (n=738)	ICD (n=298)
Age, mean (SD), y	66 (9)	66 (9)	66 (9)
Male sex	854 (82)	620 (84)	234 (79)
Current smoker	128 (12)	88 (12)	40 (13)
NYHA class			
II	952 (92)	654 (89)	298 (100)
III	84 (8)	84 (11)	0 (0)
Ischemic	661 (64)	488 (66)	173 (58)
Chronic obstructive lung disease	80 (8)	60 (8)	20 (7)
Hypertension	458 (52)	313 (50)	145 (58)
Diabetes mellitus	349 (34)	236 (32)	113 (38)
Left ventricular ejection fraction, mean (SD), %	23 (5)	23 (5)	23 (5)
Systolic BP, mean (SD), mm Hg	119 (18)	118 (17)	121 (17)
Creatinine, mean (SD), $\mu\text{mol/L}$	111 (47)	111 (47)	109 (49)
Body mass index, mean (SD), kg/m^2	28 (6)	28 (6)	28 (5)
Baseline medications			
ACE inhibitor	817 (79)	588 (80)	229 (77)
ARB	231 (22)	161 (22)	70 (23)
β -Blockers	945 (91)	675 (91)	270 (91)

Data are given as number (percentage), unless otherwise indicated. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CRT-D, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association.

MAGGIC score group were included in a multivariable Cox proportional hazards model. Logistic regression models were used to calculate the C-statistic. Kaplan-Meier survival curves were constructed for each group, starting at 6 months postdevice implant. Survival curves were compared using a log-rank test. All analyses were performed using statistical software from SAS, Inc (Version 9.4; Cary, NC). A significance level of 0.05 was used.

Results

Baseline Patient Characteristics

Baseline characteristics of the study cohort are summarized in Table 1. Of the 1798 patients enrolled into RAFT, 696 were not implanted with devices capable of the diagnostics required for the analysis and were, therefore, excluded. Another 66 patients were excluded because of insufficient follow-up data and unavailable device and/or laboratory data. A final total of 1036 patients (82% men) with a mean age of 66 ± 9 years were included in the analysis. Most (92%) of patients had mild HF symptoms (New York Heart Association class II) at study enrollment, and the mean left ventricular ejection fraction was moderate to severely impaired at $23 \pm 5\%$. Of the 1036 patients, 738 (71%) were implanted

with cardiac resynchronization therapy defibrillator devices. Most patients were on guideline-directed medical therapy; >91% of patients were treated with β -blockers, and >96% were receiving either an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker.

Predictors of Mortality

Four device diagnostic parameters and MAGGIC score were significant predictors of mortality in a univariable analysis. The HRs for these parameters were as follows: intermediate MAGGIC score versus low MAGGIC score: HR, 2.46; 95% CI, 1.29 to 4.68; $P=0.006$; high MAGGIC score versus low MAGGIC score: HR, 6.36; 95% CI, 3.35 to 12.06; $P<0.001$; AF flag: HR, 2.38; 95% CI, 1.55 to 3.65; $P<0.001$; positive FI: HR, 2.62; 95% CI, 1.81 to 3.79; $P<0.001$; activity flag: HR, 2.29; 95% CI, 1.63 to 3.22; $P<0.001$; and ICD shock flag: HR, 2.23; 95% CI, 1.40 to 3.55; $P=0.001$. In a multivariable analysis, ICD shock dropped off, and the following remained independent predictors of mortality: intermediate to high MAGGIC scores, positive FI, AF flag, and activity flag (Table 2).

A device-integrated diagnostic (DID) parameter was derived to include FI, AF, and activity flags such that patients were considered DID positive (DID+) when FI was positive and either AF flag or activity flag was positive; otherwise, patients

Table 2. Multivariable Analysis of Predictors for Mortality

Variable	Hazard Ratio (95% CI)	P Value
MAGGIC score		
0–16
17–24	2.13 (1.11–4.08)	<0.001
>24	4.61 (2.38–8.93)	...
FI		
FI–*	...	<0.001
FI+†	2.00 (1.36–2.92)	...
AF flag‡	1.70 (1.10–2.64)	0.018
Activity flag§	1.54 (1.08–2.20)	0.018

There were no significant interaction terms. AF indicates atrial fibrillation; FI, fluid index; FI+, FI positive; FI–, FI negative; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure.

*FI– denotes ≤14 days above intrathoracic impedance threshold of 60 Ω-days.

†FI+ denotes >14 days above intrathoracic impedance threshold of 60 Ω-days.

‡AF flag denotes ≥6 hours of AF on at least 1 day.

§Activity flag denotes mean activity <60 min/d for ≥1 week.

were designated as DID negative (DID–). The number of deaths stratified by MAGGIC score group and DID status, along with the percentage of patients, is reported in Table 3 and illustrated in Figure 2. C-statistics were computed for MAGGIC alone and for MAGGIC in combination with DID and were 0.682 and 0.708, respectively.

Survival Curves

When patients were divided into 3 cohorts based on low, intermediate, and high MAGGIC scores, patients with high MAGGIC scores had lower 3-year survival rates than those with intermediate or low scores (73.0% versus 88.1% versus 96.8%; *P*<0.001) (Figure 3A). A positive DID alone was also strongly associated with lower survival compared with those who were DID negative (63.2% versus 88.8%; *P*<0.001) (Figure 3B).

When the MAGGIC score cohorts were stratified according to the presence of the integrated metric (DID) derived using 3

Table 3. Mortality Stratified According to MAGGIC Score and DID Status

MAGGIC Score			
DID Status	<17	17–24	>24
All	11 (4.4)	58 (10.5)	64 (27.4)
DID+	1 (16.7)	11 (22.5)	21 (52.5)
DID–	10 (4.1)	47 (9.4)	43 (22.2)

Data are given as number (percentage) of deaths. DID indicates device-integrated diagnostic; DID+, DID positive; DID–, DID negative; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure.

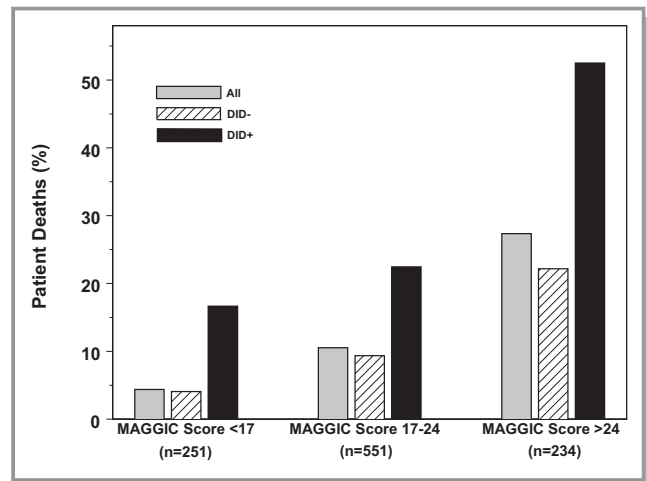


Figure 2. Illustration of patient deaths in various Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) groups and with device-integrated diagnostic (DID)–negative (DID–) and DID-positive (DID+) status.

significant device parameter flags described above, no prognostic effect was observed among patients with low-risk MAGGIC scores. However, among those with intermediate-risk MAGGIC scores, DIDs further distinguished risk such that the time to death for DID+ patients was shorter than for DID– patients (HR, 2.82; 95% CI, 1.46–5.44; *P*=0.002) (Figure 4A). Similarly, DID was also able to identify the most fragile patients among the high-risk MAGGIC cohort, with a much shorter time to death in DID+ patients compared with DID– patients (HR, 3.02; 95% CI, 1.79–5.11; *P*<0.001) (Figure 4B). The interaction between MAGGIC score and DID was not significant (*P*=0.876).

Discussion

This study demonstrates the additional prognostic value of implantable DIDs over clinical parameters in the prediction of mortality in intermediate- to high-risk patients with HF. Specifically, a combination of device parameters with a well-validated clinical model, such as MAGGIC, can help to further stratify patients at the highest mortality risk. This observation may have significant implications in an era in which HF remains a lethal pandemic, despite significant strides in medical and device therapy; and identifying patients at highest risk with the highest possible specificity remains an unmet need. Several clinical prediction models have been developed to identify patients who are at highest risk and may need more immediate medical attention. Unfortunately, these models have moderate specificity in identifying high-risk patients and are based on clinical signs and symptoms that often present late in the course of a patient’s illness, which impairs our ability to react in a

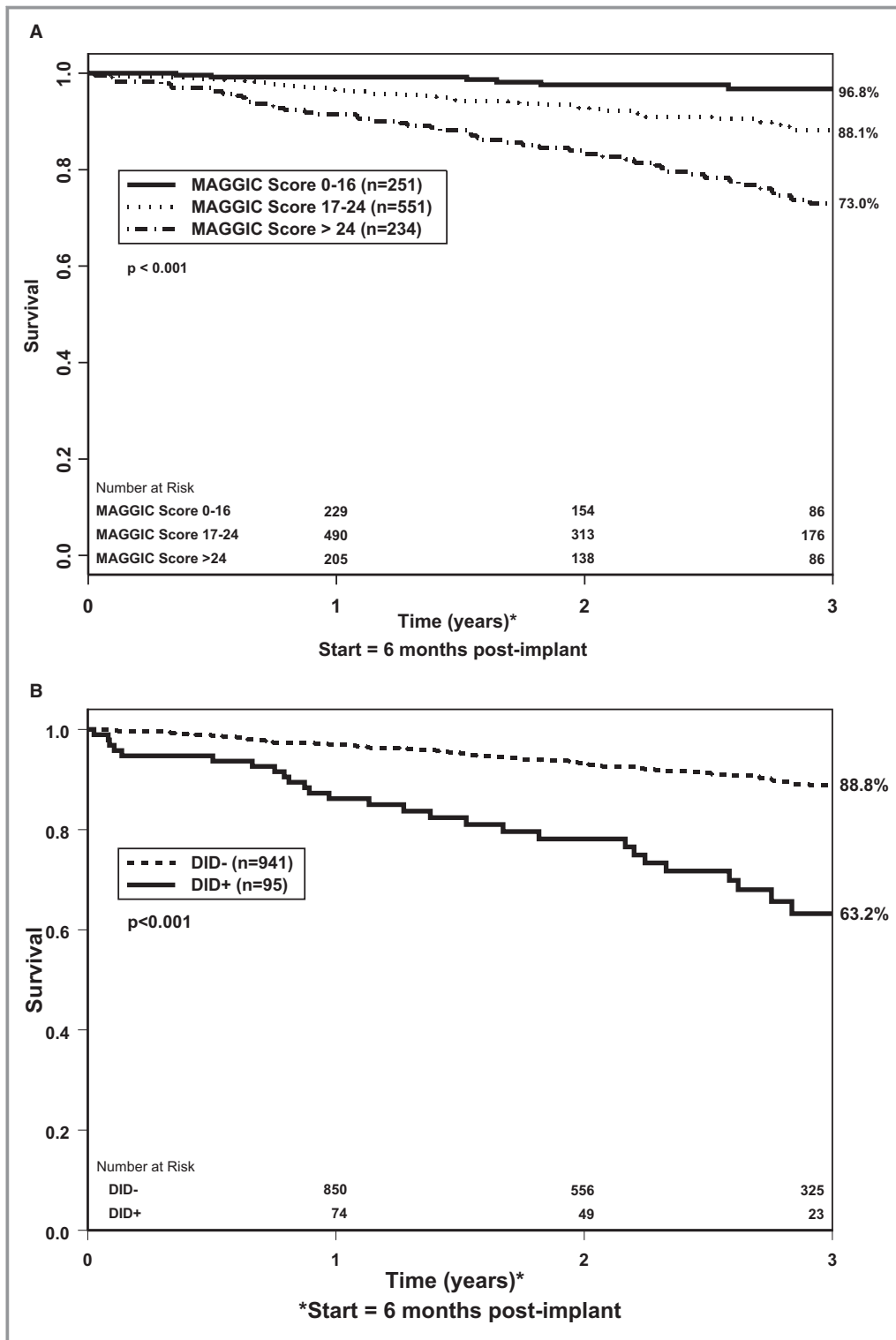


Figure 3. Kaplan-Meier survival analysis for all-cause mortality stratified according to Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score classification (A) and device-integrated diagnostic (DID) classification (B). DID+ indicates DID positive; DID–, DID negative.

timely manner. Thus, better-performing models with capability to reflect patient status on a more dynamic basis are needed to allow for timely intervention in patients with HF.

It is well established that widespread use of ICDs, both with and without cardiac resynchronization therapy, has significantly improved survival and functional capacity in the

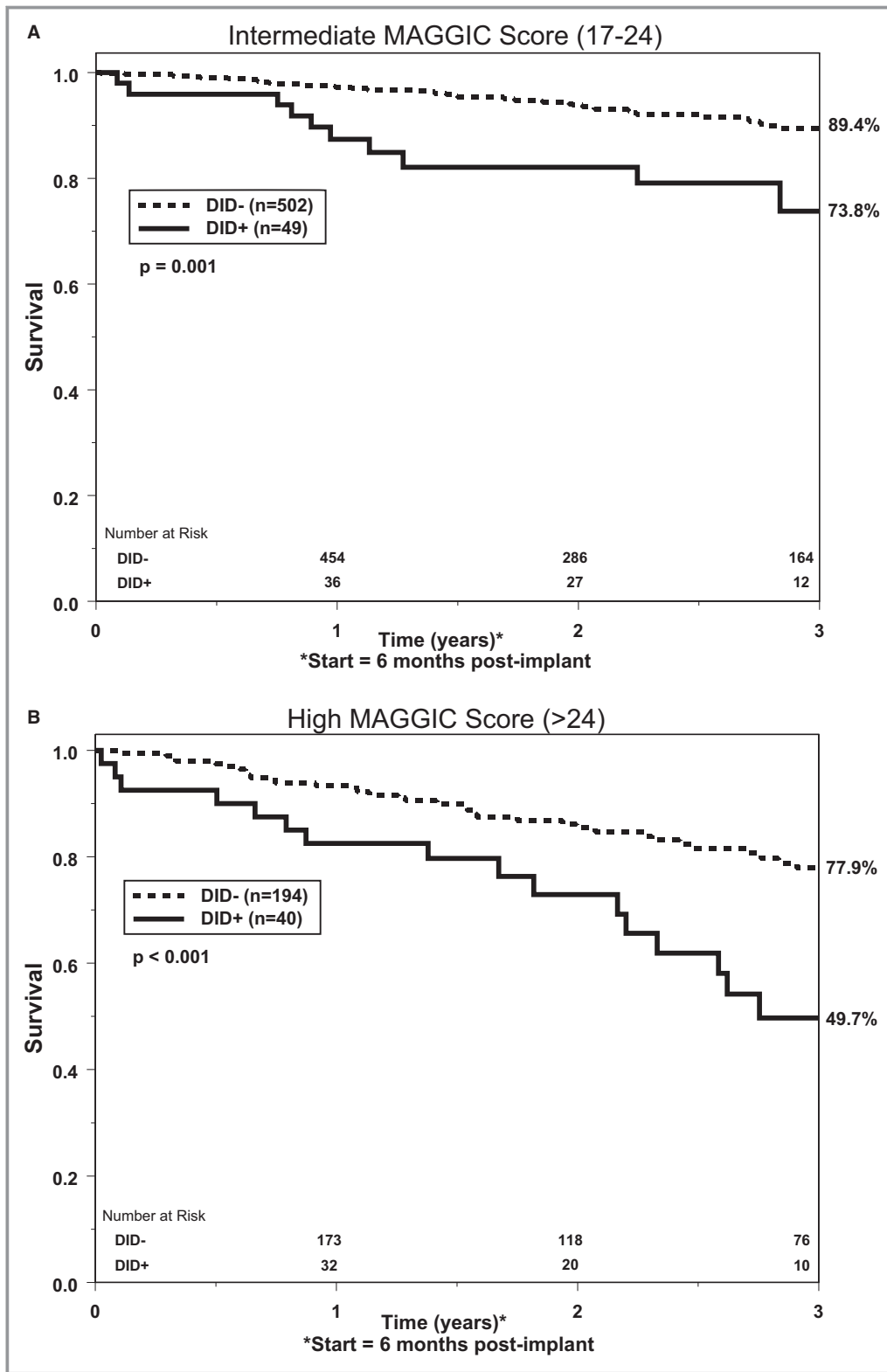


Figure 4. Kaplan-Meier survival curves in intermediate Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score (A) and high MAGGIC score (B) groups stratified according to device-integrated diagnostic (DID) positive (DID+) or DID negative (DID-). The combined prognostic value of a positive fluid index plus either an atrial fibrillation or an activity flag is observed in both groups, but most evident in the high-risk cohort.

population with HF.^{17,19–24} Modern implantable cardiac devices have the added benefits of sensors, memory, and computing power that have provided a novel and convenient means of monitoring and evaluating patients remotely.^{12,13} Although individual diagnostic parameters may be of marginal value, integration of multiple diagnostic parameters applied in the context of a particular patient's clinical profile may provide more specific prognostic information.

In this substudy of RAFT, we examined the utility of combining a clinical risk score and DID parameters for prognostication. Among the HF prediction models, we chose the MAGGIC score because it is an easily accessible, commonly used clinical prediction model that was derived in a large, heterogeneous population of almost 40 000 patients with HF and validated in a separate cohort of >51 000 patients.^{4,5} In this analysis, the RAFT cohort was stratified according to MAGGIC score into low-, intermediate-, and high-risk groups. Following multivariable analysis, DID, which accounted for FI, activity, and AF burden, along with intermediate to high MAGGIC scores were identified as independent predictors of increased mortality. When DID was analyzed within the 3 MAGGIC score cohorts, patients with intermediate- and high-risk scores who were also DID+ had a significantly higher 3-year mortality. The discriminating effect of DID on mortality risk was particularly pronounced in the high-risk group, demonstrating a 30% higher mortality rate over the same follow-up period. These data suggest that, when used in conjunction with a clinical prediction model, a combination of device parameters (ie, FI, AF, and activity) can provide powerful incremental prognostic information in patients who are already at particularly high risk of death on the basis of their clinical profile. In this case, the application of this combination of device diagnostics within the clinical context provided by the MAGGIC score may account for the significant difference in predictive power. Not surprisingly, these implantable device diagnostics were not discriminative in the low-risk MAGGIC group given that their mortality rate is already low.

The use of additional clinical risk factors to enhance the predictive power of clinical diagnostic tools is an established and effective means of improving the utility and interpretability of commonly used diagnostic tests. The D-dimer for deep vein thrombosis, high-sensitivity troponin, and the treadmill exercise test for ischemic chest pain are just a few routinely used examples. In our study, the application of the combination of device diagnostics within the clinical context provided by the MAGGIC score helped to further improve overall predictive power. Not surprisingly, these implantable device diagnostics were not discriminative in the low-risk MAGGIC group given that their mortality rate is already low. Nevertheless, the fact that device diagnostic parameters have incremental predictive power on top of a well-developed MAGGIC model based solely on clinical parameters suggests that it may be possible to develop better predictive models by

integrating clinical and device parameters into a single model. Furthermore, because device diagnostic data are more dynamic and can now be transmitted via remote monitoring systems, such combined models would also be more responsive and adapt to a particular patient's changing risk state more readily. We believe that such high-performing and dynamic models are needed to identify patients at highest risk with greater specificity and allow for a timely intervention.

Implantable device diagnostics may improve our ability to identify individuals in need of more immediate intervention. With the advent of remote monitoring technology, these device parameters can be monitored frequently (eg, monthly or biweekly) and alert the need for medical attention without the need for in-person assessment. This has important implications for many patients, especially for those living in remote areas. Therefore, although device-derived data can never fully replace clinical assessment, this technology, especially when combined with clinical data (eg, in an electronic medical record system in which clinical and device data can be merged as inputs to a combined model), may capture the dynamic risk state of the patient more readily. This, in turn, could greatly facilitate more efficient management the patient population with HF, who is rapidly outgrowing the human resources needed to manage them by conventional means.

Limitations

Although the results of this study are promising, it has a few limitations and is susceptible to the usual challenges of any retrospective analysis and unknown confounding variables. For example, although all deaths were adjudicated by a clinical event committee, noncardiac deaths caused by other conditions, such as pneumonia, may still be difficult to differentiate from HF, which can reduce intrathoracic impedance and overestimate the effect of a positive FI and, hence, DID+. Last, although the MAGGIC score has been validated in all patients with HF, including those with preserved ejection fraction, the RAFT cohort was a population that consisted entirely of patients with moderately to severely reduced systolic function (ejection fraction $\leq 35\%$). Therefore, the results of this study may not apply to those with HF with preserved ejection fraction.

Conclusions

This study suggests that implantable device diagnostics integrating FI trends, AF burden, and activity level may provide significant incremental prognostic value to clinical prediction scores in intermediate- to high-risk patients with mild to moderate HF. Further prospective studies are needed to validate this finding and determine whether early intervention guided by these measurements can modify risk and decrease mortality.

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Disclosures

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