Assessment Of Patient Selection Bias in Prospective Studies of Heart Failure

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Highlights

- Exploration of the clinical differences and outcomes between patients who agree to full participation in an observational clinical study, partial participation or usual care
- Significant differences in clinical characteristics and outcomes were observed depending on how patients were enrolled
- Generalization performance of multivariable models is influenced by the enrollment strategy

	Full Participation (N=428)	Partial Participation (N=110)	Routine Care (N=243)
Age (years)	74 [66 - 81]†	77 [68 - 84]*	77 [69 - 83]*†
Men (%)	302 (70.4%)	63 (57.3%)†	162 (66.7%)
Clinical history			
Prior Myocardial infarction	45 (10.6%)	21 (19.6%)*	43 (18.4%)*
Prior Stroke	33 (9.1%)	11 (11.0%)	28 (20.9%)*†
Peripheral vescular disease	27 (6.5%)	7 (6.6%)	25 (10.8%)
Device (ICD, PPM, CRT, CRT-D)	61 (14.2%)	17 (15.5%)	28 (11.5%)
Lung disease (COPD, Asthma, etc)	127 (30.0%)	27 (25.0%)†	44 (18.8%)
Diabetes	135 (31.8%)	40 (36.4%)	72 (30.1%)
Chronic kidney disease	87 (24.2%)†	22 (22.7%)	45 (31.3%)
Liver disease	12 (3.4%)	3 (3.2%)	4 (3.3%)
Gastro-intestinal disease	30 (8.3%)	12 (12.5%)	20 (15.4%)
Joint or connective tissue disease	102 (24.1%)†	29 (26.6%)	50 (21.4%)
Cancer	44 (10.4%)	5 (4.6%)	21 (9.0%)
CCI	2 [1 - 4]	3 [2 - 5]	2 [1 - 4]
Heart rate (bpm)	89 [72 - 110]†	90 [72 - 114]	91 [75 - 110]
Heart rhythm			
Sinus rhythm	131 (30.5%)	32 (29.1%)	71 (29.2%)†
Atrial fibrillation	155 (36.1%)†	49 (44.5%)	83 (34.2%)
Other rhythm	143 (33.3%)†	29 (26.4%)	89 (36.6%)
Systolic BP (mmHg)	127 [112 - 147]	130 [116 - 147]	128 [113 - 142]†
Diastolic BP (mmHg)	76 [64 - 86]†	75 [64 - 85]	77 [64 - 89]
Worst NYHA in last 7 days			
Class II	43 (13.4%)	10 (13.7%)	3 (7.9%)
Class III	207 (64.3%)	50 (68.5%)	23 (60.5%)
Class IV	71 (22.0%)†	12 (16.4%)	10 (26.3%)
HF medication			
ACE inhibitor	217 (50.6%)	53 (48.2%)	170 (70.0%)*
Beta blocker	259 (60.4%)	75 (68.2%)	192 (79.0%)*
MRA	144 (33.6%)	43 (39.1%)	141 (58.0%)
Loop diuretic	416 (97.0%)†	110 (100.0%)†	226 (93.0%)
Thiazide	284 (66.2%)	73 (66.4%)	189 (77.8%)
Digoxin	116 (27.0%)	38 (34.5%)	141 (58.0%)
NT-proBNP	4924 [2010 - 10085]†	3942 [1962 - 9803]	5288 [2476 - 10912]†
30 day readmission	8 (3.0%)	3 (2.9%)	15 (7.8%)
1 year death	41 (20.4%)	22 (23.4%)	65 (33.3%)*

Table 1. Results of key characteristics by study participation level, represented as median [IQR] or # (%). Missing data were excluded. * Indicates significant (p<0.05) difference compared with Full Participation. † Variables that demonstrated significant univariable correspondence with 1-year mortality and were included as candidate terms in the multivariable model

OPERA-HF: a prospective, observational study

Full Participation	Patients allowed investigators to have access to clinical notes and agreed to have additional tests (e.g., questionnaires and low-intensity physical tests such as get-up-and-go)
Partial Participation	Patients allowed investigators to have access to clinical notes
Routine Care	Clinical notes reviewed via routine audit

Inclusion criteria:

- patients hospitalized for or with heart failure.
- age >18 years,
- treatment with loop diuretics
- at least one of the following:
  - left ventricular ejection fraction ≤40%
  - left atrial dimension >4.0 cm
  - NT-ProBNP
    - >400 pg/mL (if sinus rhythm)
    - >1200 pg/mL (if atrial fibrillation).

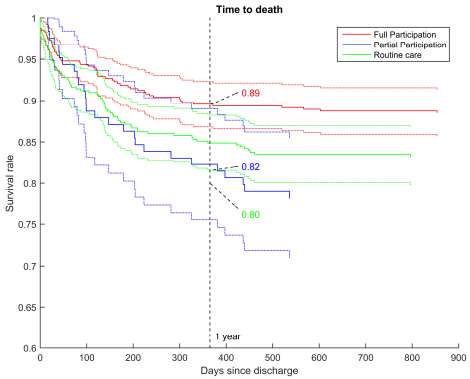

Figure 1. Kaplan-Meier survival curve for time to death (95% CI) for the three participation levels.

Statistical analysis:

Relative risk, for binary variables, and Wilcoxon rank-sum tests, for continuous variables, were estimated to compare data at different study participation levels (Table 1).

Univariable logistic regression was used to select parameters (p<0.05; indicated in Table 1) to build a multivariable logistic regression model for the 1-year death outcome using full participation level patient data.

Generalization performance was estimated using 10-fold cross validation. Also, the partial participation and routine care data were used for two more evaluations of the model (results in Table 2).

Training \ Evaluation	F.P.	P.P.	R.C.
Full Participation	0.83	0.61	0.67

Table 2. Generalization performance (AUC) evaluated per participation level

Conclusion

- Patients who agreed to participate fully:
  - had fewer comorbidities
  - were taking fewer medication
  - had a lower risk of readmission and mortality.
- Predictive models based on patients who agree to participate in trials might generalize poorly to routine clinical populations.
- Trials should be interpreted in the light of possible selection bias.
- Whether the selection bias was due to clinicians/nurses choosing which patients they thought to be appropriate or was due to patient choice requires further study.

Declaration of interest

JJGV, IS, GG, SCP, JMR and AT are employed by Philips Research. KMG, JGC and ALC have received departmental research support from Philips.

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