PCV5

# 3C-HF Prognostic Score to Predict Worsening Cardiac Function Among Congestive Heart Failure Patients in United States and Europe

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## Background

- Congestive heart failure (CHF) remains a significant cause of morbidity and mortality despite advances in cardiovascular treatment.[1]
- The use of prognostic scores is important to guide CHF management and treatment decisions.
- Despite a myriad of scoring approaches in practice, not all variables to calculate these scores are readily available.
- The New York Heart Association Functional Classification relies on patient- and physician-assessed physical activity limitations, but is often not obtainable for population research in structured electronic medical records (EMR) or health plan claims data sources.[2]
- The Cardiac and Comorbid Conditions HF (3C-HF) score has an advantage of incorporating commonly recorded data from routine visits (e.g., comorbidities and treatment history) to predict 1-year mortality in HF patients.[3,4]
- This research examines deployment of the 3C-HF score in readily available EMR or payor claims data in the United States (US), France, and the United Kingdom (UK).

## Objectives

- To explore the ability to use the 3C-HF across multiple data sources and compare the distribution of prognostic factors between patients from Europe and the US
- To explore the utility of the 3C-HF score in predicting worsening of cardiac morbidity, as estimated by hospitalization and recurrent myocardial infarction (MI)

## Methods

### Data Source

- US
  - Patient data were extracted from the HealthVerity™ Marketplace, including 1 EMR source and 1 linked institutional and pharmacy claims data source between Jan 1, 2014 and Jun 30, 2019.
    - HealthVerity™ has the most complete coverage of US healthcare, consumer, and purchase data, with access to over 330 million patients and 30 billion transactions.[6]
    - Private Source (PS) 42 is a multispecialty ambulatory EMR of 60 million unique patients; PS1734 is an institutional claims source and a provider of claims source data covering 140 million patients (PS34) that has been linked to PS17, a multi-payor pharmacy transaction database.
- Europe
  - Data were extracted from THIN® UK and France databases between July 1, 2016 and June 30, 2019.
    - THIN (The Health Improvement Network®) is an anonymized EMR powered by Cegedim Health Data® division. THIN® is a large European database, collecting data at the physicians' level.
- Data sets were converted into the Observational Medical Outcomes Partnership Common Data Model, v5.
- Analyses were conducted in SHYFT Quantum v7.1.1. Supplemental analyses were conducted using Microsoft SQL Server Studio 2017 and R v3.5.2

### Study Design

- Inclusion/exclusion criteria (Figure 1):
  - ≥ 6 months continuous activity post-index for EMR data, continuous enrollment for claims (HV PS1734)
  - Patients with ≥ 2 diagnoses of CHF (I50.xx), or ≥ 1 diagnosis of CHF (I50.xx) and any evidence of CHF treatment based on drug National Drug Code or Anatomical Therapeutic Chemical codes for beta blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB), diuretics (furosemide, loop diuretics, other), calcium channel blockers, neprilysin inhibitor (sacubutril/valsartan), and hyperpolarization-activated cyclic nucleotide-gated channel inhibitor (ivabradine)
  - Age ≥ 18 years
  - Index date: earliest diagnosis code for CHF

Figure 1: Study Cohort Selection

| Country | US | | France | UK |
|---|---|---|---|---|
| Database | PS42 | PS1734 | THIN® | THIN® |
| Total Population, N | 71,364 | 75,114 | 61,389 | 51,718 |
| ≥ 2 diagnoses of CHF or 1 CHF diagnosis and 1 CHF drug, N | 9,179 | 4,718 | 21,950 | 20,383 |
| Age ≥18 years, N | 9,171 | 4,718 | 21,943 | 20,347 |
| ≥ 6 months continuous activity post-index date, N | 8,421 | 3,598 | 16,703 | 18,179 |
| Patients included in the analysis, N | 8,421 | 3,598 | 16,703 | 18,179 |

### Study Measures

- Baseline patient characteristics: age, gender, frequency of visits to clinician's office, common cardiovascular comorbidities and treatments
- 3C-HF scores were assessed using baseline characteristics (e.g., comorbidities and treatment history) between start of observation and 90 days post-index.[3,4]
  - Due to limited comorbidity data available in patients aged > 70 years, scoring and outcomes assessments were conducted for patients aged < 70 years in UK and France. US scores did not incorporate age.
- Count of post-index MI overall and by 3C-HF score above and below median
  - First recorded MI in US data, secondary MI in France and UK data
- Count of post-index hospitalizations overall and by 3C-HF score above and below median
  - Assessed for US and France populations only

### Analyses

- Data are reported as mean, median, and standard deviation.
- Time to event analyses were performed using the Kaplan-Meier method.
  - Time to first instance of MI from index, factored by 3C-HF score above and below median
    - First recorded MI in US data, secondary MI in France and UK data
  - Time to first instance of hospitalization from index, factored by 3C-HF score above and below median
- Cox proportional hazards model
  - 1-year MI post-index
    - First recorded MI in US data, secondary MI in France and UK data
  - 1-year hospitalization post-index
    - Assessed for US and France populations only
    - Covariates: age, gender, prior MI event, 3C-HF scores (above/below median), history of chronic obstructive pulmonary disease (COPD)/asthma
- K-means clustering was conducted for the US, UK, and France populations.
  - Covariates: gender, prior MI event, 3C-HF score, history of COPD/asthma, dyslipidemia, peripheral arterial disease (PAD), and treatment history (by drug class, by prescribing specialty)
  - As a starting point, k was defined as $\sqrt{n}$.
  - Number and size of potential patient clusters was calculated.

## Results

Table 1: Baseline Demographics and Clinical Characteristics, by Country

| Country | US | | France | UK |
|---|---|---|---|---|
| Database | PS42 | PS1734 | THIN® | THIN® |
| N | 8,421 | 3,598 | 16,703 | 18,179 |
| Age, mean (SD) | 70.5 (11.7) | 73.8 (11.8) | 79.7 (11.8) | 77.3 (12.7) |
| Gender, n (%) | | | | |
| Male | 4,255 (50.4) | 1,716 (47.4) | 9,308 (55.7) | 10,293 (56.6) |
| Female | 4,157 (49.3) | 1,765 (49.1) | 7,395 (44.3) | 7,885 (43.4) |
| Missing | 29 (0.3) | 117 (3.5) | – | – |
| Common cardiovascular comorbidities, n (%) | | | | |
| Cardiomyopathy | 1,563 (18.6) | 344 (9.6) | 647 (3.9) | 317 (1.7) |
| MI | 216 (2.6) | 135 (3.85) | 784 (4.7) | 1,129 (6.2) |
| Type 2 Diabetes | 2,239 (26.6) | 599 (16.6) | 2,352 (14.1) | 701 (3.9) |
| Hypertension | 3,224 (38.3) | 1,210 (33.6) | 6,902 (41.3) | 1,269 (7.0) |
| CKD | 1,527 (18.1) | 964 (26.8) | 199 (1.2) | 89 (0.5) |
| Dyslipidemia | 3,794 (45.1) | 715 (19.9) | 2,100 (12.6) | 326 (1.8) |
| PAD | 463 (5.5) | 207 (5.8) | 383 (2.3) | 114 (0.6) |
| HFrEF | 5,716 (67.9) | 1,337 (37.2) | 161 (1.0) | 101 (0.6) |
| COPD / Asthma | 1,338 (15.9) | 529 (14.7) | 1,787 (10.7) | 930 (5.1) |
| Common cardiovascular treatments, n (%) | | | | |
| Beta blocker | 5,679 (67.4) | 2,064 (57.4) | 9,451 (56.6) | 9,979 (54.9) |
| ACE inhibitors | 3,139 (37.3) | 1,175 (32.7) | 5,845 (35.0) | 8,178 (45.0) |
| ARB | 1,786 (21.2) | 796 (22.1) | 3,388 (20.3) | 2,888 (15.9) |
| Ivabradine | – | – | 407 (2.4) | 329 (1.8) |
| Sacubitril/Valsartan | – | 4 (0.1) | 147 (0.9) | 81 (0.4) |
| Calcium–channel blocker | 2,578 (30.6) | 1,203 (33.4) | 3,028 (18.1) | 4,308 (23.7) |
| Diuretics excluding Sulfonamide | 3,608 (42.8) | 1,457 (40.5) | 2,571 (15.4) | 4,405 (24.2) |
| Sulfonamide/loop diuretics | 4,721 (56.1) | 1,604 (44.6) | 8,211 (49.2) | 8,401 (46.2) |
| Mean cardiology visit pre–index | 1.8 | 18.0 | 2.5 (2.1) | – |
| Mean GP visit pre–index | 3.9 | 10.0 | 5.5 (SD 5.8) | 18.4 (SD 16.7) |
| 3C–HF score, mean (SD) | 8.7 (7.1) | 11.1 (5.1) | 15.8 (4.3) | 17.1 (3.8) |
| 3C–HF score, median | 12 | 8 | 16 | 17 |
| 3C–HF score – above median, n (%) | 5,708 (67.8) | 1,504 (41.8) | 8,958 (54.0) | 10,167 (56.0) |

CKD, chronic kidney disease; HFrEF, heart failure w/ reduced ejection fraction; SD, standard deviation

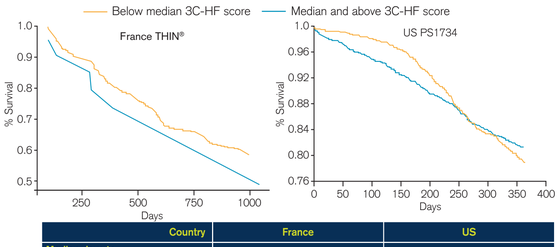
Table 2: 3C-HF Scores and Components, by Country

| Country | US | | | | France | | UK | |
|---|---|---|---|---|---|---|---|---|
| Database | PS42 | | PS1734 | | THIN® | | THIN® | |
| N at baseline | 8,421 | | 3,598 | | 16,703 | | 18,179 | |
| Variable | Multiplier | Patient count | % | Patient count | % | Patient count | % | Patient count | % |
| Atrial fibrillation | 7 | 1,413 | 16.8 | 439 | 12.2 | 3,925 | 23.5 | 1,953 | 10.7 |
| Severe valve disease | 7 | 138 | 1.6 | 136 | 3.8 | 316 | 1.9 | 675 | 3.7 |
| Diabetes w/ complications | 6 | 843 | 10.0 | 281 | 7.8 | 75 | 0.4 | 694 | 3.8 |
| Anemia | 4 | 309 | 3.7 | 273 | 7.6 | 690 | 4.1 | 637 | 3.5 |
| Hypertension | -4 | 1,412 | 16.8 | 862 | 24.0 | 6,902 | 41.3 | 1,269 | 7.0 |
| No beta blocker | 4 | 6,318 | 75.0 | 2,062 | 57.3 | 15,503 | 92.8 | 17,727 | 97.5 |
| No ACE inhibitor | 8 | 6,926 | 82.3 | 2,256 | 62.7 | 15,489 | 92.7 | 17,794 | 97.9 |
| Age < 40 | 0 | – | – | – | – | 77 | 0.5 | 170 | 0.9 |
| Age 40–49 | 1 | – | – | – | – | 223 | 1.3 | 392 | 2.2 |
| Age 50–59 | 2 | – | – | – | – | 796 | 4.8 | 1,215 | 6.7 |
| Age 60–69 | 3 | – | – | – | – | 1,952 | 11.7 | 2,511 | 13.8 |
| Age 70–79 | 4 | – | – | – | – | 3,844 | 23.0 | 4,827 | 26.6 |
| Age 80–89 | 5 | – | – | – | – | 6,483 | 38.8 | 6,271 | 34.5 |
| Age 90–99 | 6 | – | – | – | – | 3,226 | 19.3 | 2,709 | 14.9 |
| Age ≥ 100 | 7 | – | – | – | – | 102 | 0.6 | 84 | 0.5 |

Table 3: Post-index Hospitalization and MI, by Country

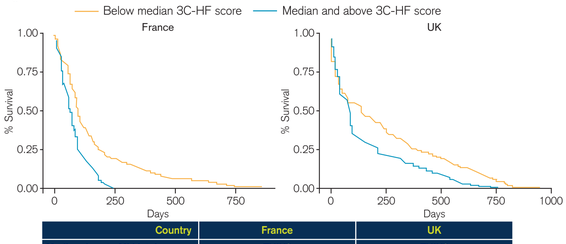
| Country | US | | France | UK |
|---|---|---|---|---|
| Database | PS42 | PS1734 | THIN® | THIN® |
| MI, n (%) | 158 (1.9) | 133 (3.7) | 869 (5.2) | 1,416 (7.8) |
| Hospitalization, n (%) | – | 1,204 (33.5) | 3,908 (23.4) | – |

Figure 2: Kaplan-Meier Assessment of Post-index Hospitalization for US and France Populations




| Country | France | US |
|---|---|---|
| Median days to hospitalization/database | THIN® | PS1734 |
| Below median | – | – |
| Median and above | 1,043 | – |

Figure 3: Kaplan-Meier Assessment of Post-index Secondary MI for France and UK Populations




| Country | France | UK |
|---|---|---|
| Median days to MI/database | THIN® | THIN® |
| Below median | 99 | 138 |
| Median and above | 73 | 85 |

## Summary

- Average patient age was lower in the US data sources (71-74 vs. 77-80) (Table 1).
  - Both France EMR and UK general practitioner data sources had relatively lower rates of cardiovascular comorbidity than the US claims (PS1734) and EMR (PS42) data sources.
  - Cardiologist visits were highest in the US claims data when compared to the French data (could not be assessed in UK data).
- The mean 3C-HF scores ranged from 15.8 in France to 17.1 in the UK and 8.7 and 11.1 in the US.
  - Lower US 3C-HF scores were in part driven by absence of age in scoring, and in PS42 being an outpatient ambulatory EMR data source (Table 2).
  - Higher scores in UK and France were largely driven by differences in prescribing of ACE inhibitors, ARB, and beta blockers.
- Rates of post-index hospitalization were higher in the US claims data (PS1734) when compared to France (could not be assessed in UK and US PS42 data) (Table 3).
  - Rates of post-index MI were higher in France and UK. Findings are consistent with baseline 3C-HF score and higher recorded rates of prior MI at baseline.
- Availability of prior MI history was robust in France and UK data sources, allowing for Kaplan-Meier assessment of post-index secondary MI risk (Table 3).
- The association of higher 3C-HF scores with MI was significant, with median time to secondary MI ranging from 73-85 days for above-median scores and 99-138 days for below-median scores, respectively (Figure 3).
  - In the US, median time to first recorded MI post-index was not reached within the observation period and could not be assessed.
  - US claims (PS1734) showed a trend towards shorter time to MI in patients with above-median 3C-HF score (data not shown).
- Cox proportional hazards assessment of European data confirmed significance of 3C-HF association with 1-year post-index hospitalization and MI (data not shown).
  - In France, post-index hospitalization was associated with above-median 3C-HF score and history of COPD/asthma. Post-index MI was associated with COPD/asthma and above-median 3C-HF score, as well as prior MI history.
  - In the UK, post-index MI was significantly associated with prior MI and COPD/asthma. While 3C-HF score was not significant, this was likely due to delayed curve separation on Kaplan-Meier analysis (Figure 3).
  - In the US data sources, time to first year MI and hospitalization in PS1734 and PS42 were associated with pre-index MI. In US claims PS1734, other associations were not conclusive, likely due to Kaplan-Meier curves not reaching median.
- K-Means showed evidence of 5 distinct clusters, driven by comorbidities and treatment history (analysis not shown).
  - In France, drivers of difference included cardiovascular comorbidity (dyslipidemia, prior MI, PAD), as well as general practitioner prescribing of ACE inhibitors, ARB, and calcium channel blocker agents.
  - US factors were driven by ACE inhibitor, ARB, and beta blocker utilization.

## Limitations

### Study Limitations

- Ejection fraction was only available for US EHR data. With only a fifth of patients with ejection fractions < 20%, its role in calculating risk score was limited. The next steps include exploration of the impact of greater variation in ejection fraction on risk score.
- US 3C-HF scores did not incorporate age. Future assessments will refine scores to explore the impact of age.
- Comorbidity capture in patients ≥ 70 was limited in the UK and France data, limiting score calculations to patients < 70 years old. Despite only focusing on patients < 70 years of age, robust associations with 3C-HF scores and outcomes were evident.
- In the UK, data source was GP and outpatient only. In the US, EMR source PS42 was outpatient only.

## Conclusions

- 3C-HF score enables rapid and robust assessment of worsening cardiac morbidity for determining risk of future MI and hospitalization using variables that are readily available during patient visits,.
- Differential patterns in 3C-HF score were observed between the US vs. France and UK. These patterns were partially driven by differences in ACE inhibitor, ARB, and beta blocker utilization.
- Initial results of clustering show potential value in identifying high-risk subgroups beyond demographics and comorbidity.
- Future application could be to integrate 3C-HF score assessment during routine visits to ascertain prognosis and inform treatment decisions.

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### Disclosures

ER, RB, AG, AS, JR, and BL are employees of Medidata Solutions.
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