ORIGINAL ARTICLE

Educational status affects prognosis of patients with heart failure with reduced ejection fraction: A post-hoc analysis from the WARCEF trial

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Funding information
National Institute of Neurological Disorders and Stroke, Grant/Award Number: U01-NS-039143 to Dr. Thompson and U01-NS-043975 to Dr. Homma

Abstract

Aims: The influence of social determinants of health (SDOH) on the prognosis of Heart Failure and reduced Ejection Fraction (HFrEF) is increasingly reported. We aim to evaluate the contribution of educational status on outcomes in patients with HFrEF.

Methods: We used data from the WARCEF trial, which randomized HFrEF patients with sinus rhythm to receive Warfarin or Aspirin; educational status of patients enrolled was collected at baseline. We defined three levels of education: low, medium and high level, according to the highest qualification achieved or highest school grade attended. We analysed the impact of the educational status on the risk of the primary composite outcome of all-cause death, ischemic stroke (IS) and intracerebral haemorrhage (ICH); components of the primary outcome were also analysed as secondary outcomes.

Bernadette Corica and Giulio Francesco Romiti have contributed equally to the paper.

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Educational status in HFrEF.

Results: 2295 patients were included in this analysis; of these, 992 (43.2%) had a low educational level, 947 (41.3%) had a medium education level and the remaining 356 (15.5%) showed a high educational level. Compared to patients with high educational level, those with low educational status showed a high risk of the primary composite outcome (adjusted hazard ratio [aHR]: 1.31, 95% confidence intervals [CI] 1.02–1.69); a non-statistically significant association was observed in those with medium educational level (aHR: 1.20, 95%CI: .93–1.55). Similar results were observed for all-cause death, while no statistically significant differences were observed for IS or ICH.

Conclusion: Compared to patients with high educational levels, those with low educational status had worse prognosis. SDOH should be considered in patients with HFrEF.

Clinical Trial Registration: NCT00041938.

KEYWORDS

educational level, heart failure, HFrEF, social determinants of health

1 | INTRODUCTION

Heart failure (HF) is an increasing public health issue, due to its rising prevalence worldwide.[1] Over the last decades, growing attention has been devoted to the role of social determinants of health (SDOH), acknowledging higher incidence of HF and worse prognosis in patients with socioeconomic deprivation.[2–4]

Several SDOH have been explored in HF patients, including employment, marital status, income and educational levels.[4–7] Particularly, some studies suggested that low educational level is associated with high risk of developing cardiovascular disease, as well as mortality from heart disease and stroke[8]; moreover, educational status has also been linked with higher risk of HF-related hospital admission.[9]

Nonetheless, the association between low educational status and poor prognosis may represent an epiphenomenon of inequal access to care for HF patients,[10–12] and may also be related to the clustering of other SDOH associated with low educational status, such as low income, unemployment and unpartnered status, which have been demonstrated to be associated to higher risk of death after discharge for HF hospitalization.[13] This seems consistent with a recent study, specifically focused on patients with HF and reduced ejection fraction (HFrEF) and with recent acute decompensated HF, that highlighted how socioeconomic status (i.e., low education, low income) was associated with higher risk of HF-related readmission and mortality.[14] Nonetheless, while this evidence suggest that low educational level may be

a key factor which influence prognosis in HFrEF patients, currently, there is still uncertainty on the extent of this association.

In this study, we aimed to analyse the influence of educational status on the prognosis of HFrEF patients, through a post-hoc analysis of the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial.

2 | METHODS

Full details on the design and rationale of the WARCEF trial, outcome adjudication, follow-up and primary results of the trial have been previously published.[15,16] Briefly, between October 2002 and January 2010, the WARCEF trial enrolled 2305 adult patients (≥18 years) with HFrEF and normal sinus rhythm, no contraindication to warfarin, and a LVEF ≤35% within 3 months before randomisation. As per the double-blind, double-dummy design, patients were randomized to receive active warfarin and placebo aspirin, or active aspirin and placebo warfarin. Patients in any New York Heart Association (NYHA) functional class were included; however, as per the trial protocol, patients in NYHA I class could account for no more than 20% of the total sample size. Patients with atrial fibrillation (AF), mechanical cardiac valve, endocarditis, or an intracardiac mobile or pedunculated thrombus at baseline were excluded. Follow-up was performed at pre-specified time-point (initially with a planned maximum duration of

5 years, further extended to 6 years). Primary outcome of the trial was the composite of ischemic stroke (IS), intracerebral haemorrhage (ICH), or death from any cause. The study was performed according to the Declaration of Helsinki; all patients provided written informed consent, and the study was approved by the international review boards and ethics boards of participating centres.

2.1 | Assessment of educational levels

Educational level was collected at baseline and reported in the case report form, according to the following categorization: (i) ≤8th grade; (ii) some high school; (iii) high school graduate; (iv) some college; (v) college graduate; (vi) post-graduate education. For this analysis, we defined three groups of educational level, as follows: (i) low educational level (<8th grade, and some high school); (ii) medium educational level (high school graduate and some college); (iii) high educational level (college graduate or post-graduate education).

2.2 | Outcomes investigated

For this analysis, and consistently with the trial main analysis, we defined our primary outcome as the composite of IS, ICH or death from any cause.

As secondary outcomes, we additionally explored the individual components of the primary outcome (i.e., all-cause death, IS and ICH).

2.3 | Statistical analysis

Continuous variables were expressed as mean (standard deviation, SD), and differences were evaluated using the ANOVA F-test. Categorical variables were expressed as counts and percentages, and differences were assessed through chi-squared test.

Covariate-adjusted Cox-regression model was used to analyse the association between educational status and the risk of primary and secondary outcomes. All regression models were adjusted for age, sex, randomisation to warfarin versus aspirin, smoking status (current vs. ex/never), alcohol consumption, race or ethnic group, NYHA class (I-II vs. III-IV), history of hypertension, history of diabetes mellitus, history of IS/transient ischemic attack, history of myocardial infarction (MI), and marital status.

A two-sided $p < .05$ was considered statistically significant. All analyses were performed using R 4.2.3 (R Core Team, Vienna, Austria) for Windows.

3 | RESULTS

A total of 2305 patients were originally enrolled in the WARCEF trial, and 2295 (99.6%) with complete data on educational level were included in this analysis. Of these, 992 (43.2%) had low educational level (mean age 62.2 ± 11.0, females 21.6%), 947 (41.3%) had medium educational level (mean age 59.1 ± 11.7, females 19.3%), and 356 (15.5%) had a high education level (mean age 61.4 ± 10.6, females 17.4%).

Baseline characteristics according to the educational status are shown in Table 1. Patients with low educational level were older, and with a higher proportion of patients aged 65 years of older (44.1% vs. 38.8% and 30.6% in the high and medium educational level groups respectively, $p < .001$). Higher percentage of females was found in the low educational level group (21.6%), followed by medium (19.3%) and high educational level (17.4%); conversely, current smokers were more represented in low and medium educational level groups (18.6% and 19.0%, respectively vs. 12.4% in high educational level group). Current alcohol use was more frequently found in the high educational status group (30.9%) comparing to low (24.1%) and medium educational status (23.3%). Finally, a higher proportion of non-married individuals was found in the low and medium educational level groups (35.7% and 41.0%, respectively), compared to 26.4% of the high educational level group. Conversely, comorbidities at baseline were broadly balanced between groups.

3.1 | Risk of adverse events according to educational level

After a median follow-up time of 3.4 (IQR: 2.0–5.0) years, 618 (26.9%) events of the primary outcome occurred in the patients included in this analysis.

Number of events and incidence rates according to educational levels are reported in Table 2; Kaplan–Meier analysis for the risk of the primary composite outcome (Figure 1) showed higher survival for patients with high level of education (high vs. medium, $p = .055$; high vs. low, $p = .007$), while no difference was observed between medium and low educational status ($p = .32$).

The results of the multiple Cox-regression analyses for primary and secondary outcomes are reported in Table 2. Compared to patients with high educational level, those with low educational level were found at higher risk of the primary composite outcome (adjusted Hazard Ratio [aHR]: 1.31, 95% confidence intervals (CI) 1.02–1.69); some evidence, although not statistically significant, was

TABLE 1 Baseline characteristics according to educational level.

Variables, n/total (%)	Low education (n = 992)	Medium education (n = 947)	High education (n = 356)	p-value
Demographics				
Age, mean (SD)	62.2 (11.0)	59.1 (11.71)	61.4 (10.6)	**<.001**
Age ≥65 years	437 (44.1)	290 (30.6)	138 (38.8)	**<.001**
Female sex	214/992 (21.6)	183/947 (19.3)	62/356 (17.4)	.193
Race or ethnic group				
Black	93/992 (9.4)	205/947 (21.6)	34/356 (9.6)	**<.001**
Hispanic	100/992 (10.1)	54/947 (5.7)	12/356 (3.4)	
Non-hispanic white	773/992 (77.9)	665/947 (70.2)	291/356 (81.7)	
Other	26/992 (2.6)	23/947 (2.4)	19/356 (5.3)	
Non-married marital status	354/992 (35.7)	388/947 (41.0)	94/356 (26.4)	**<.001**
Physical examination				
BMI (kg/m^2), mean (SD)	28.4 (5.4)	29.8 (6.5)	29.4 (5.7)	**<.001**
Systolic BP (mmHg), mean (SD)	124.9 (18.4)	123.6 (19.4)	122.3 (18.4)	.057
Diastolic BP (mmHg), mean (SD)	74.7 (11.2)	74.2 (11.7)	73.0 (11.1)	.066
Heart rate (bpm), mean (SD)	71.9 (12.1)	72.2 (11.7)	71.4 (12.2)	.558
Medical history, n/total (%)				
History of hypertension	587/971 (60.5)	577/912 (63.3)	199/343 (58.0)	.189
History of diabetes mellitus	302/991 (30.5)	315/943 (33.4)	104/356 (29.2)	.231
History of atrial fibrillation	30/991 (3.0)	39/944 (4.1)	17/356 (4.8)	.241
History of myocardial infarction	473/990 (47.8)	457/944 (48.4)	179/356 (50.3)	.720
History of ischemic cardiomyopathy	449/990 (45.4)	393/943 (41.7)	146/356 (41.0)	.177
History of pulmonary or other embolisms	15/991 (1.5)	26/944 (2.8)	11/355 (3.1)	.098
History of ischemic stroke/TIA	114/991 (11.5)	133/945 (14.1)	47/355 (13.2)	.232
Smoking status				
Current	184/990 (18.6)	180/946 (19.0)	44/356 (12.4)	**<.001**
Ex	509/990 (51.4)	500/946 (52.9)	168/356 (47.2)	
Never	297/990 (30.0)	266/946 (28.1)	144/356 (40.4)	
Alcohol consumption				
Current	239/991 (24.1)	221/947 (23.3)	110/356 (30.9)	**<.001**
Ex	205/991 (20.7)	244/947 (25.8)	57/356 (16.0)	
Never	547/991 (55.2)	482/947 (50.9)	189/356 (53.1)	
NYHA class				
NYHA I	111/990 (11.2)	137/940 (14.6)	66/356 (18.5)	**.002**
NYHA II	558/990 (56.4)	511/940 (54.4)	196/356 (55.1)	
NYHA III	306/990 (30.9)	286/940 (30.4)	87/356 (24.4)	
NYHA IV	15/990 (1.5)	6/940 (.6)	7/356 (2.0)	
LVEF, mean (SD)	25.1 (7.6)	24.5 (7.4)	25.7 (7.4)	.059
Treatments				
Randomized to warfarin	490/992 (49.4)	487/947 (51.4)	163/356 (45.8)	.188
ACE inhibitor/ARB	979/989 (99.0)	924/944 (97.9)	350/356 (98.3)	.145
Beta blocker	889/990 (89.8)	857/944 (90.8)	312/356 (87.6)	.245

TABLE 1 (Continued)

Variables, n/total (%)	Low education (n = 992)	Medium education (n = 947)	High education (n = 356)	p-value
Aldosterone blocker	378/632 (59.8)	315/519 (60.7)	119/193 (61.7)	.888
Nitrate	239/990 (24.1)	214/943 (22.7)	89/356 (25.0)	.616
Calcium channel blocker	100/989 (10.1)	83/943 (8.8)	19/355 (5.4)	**.025**
Diuretic	807/990 (81.5)	763/944 (80.8)	281/356 (78.9)	.569
Statin	611/764 (80.0)	562/661 (85.0)	217/249 (87.1)	**.007**
Device therapy				
Pacemaker	103/991 (10.4)	133/944 (14.1)	47/356 (13.2)	**.041**
Implantable cardioverter-defibrillator	145/991 (14.6)	204/944 (21.6)	67/356 (18.8)	**<.001**

Note: Significant p-values are shown in bold.

Abbreviations: ACE, Angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; NYHA, New York Heart Association functional class; SD, standard deviation.

TABLE 2 Event count and incidence rate for the risk of primary composite outcome and for the secondary outcomes.

	Event count	Events per 100 person-years, IR (95%CI)	aHR (95%CI)	p-value
Primary composite outcome				
High education	84/356	6.0 (4.8–7.5)	Ref.	Ref.
Medium education	264/947	7.7 (6.8–8.7)	1.20 (.93–1.55)	.159
Low education	270/992	8.4 (7.4–9.4)	1.31 (1.02–1.69)	**.037**
Secondary outcomes				
All-cause death				
High education	65/356	4.7 (3.6–6.0)	Ref.	Ref.
Medium education	227/947	6.6 (5.8–7.5)	1.30 (.98–1.72)	.074
Low education	235/992	7.3 (6.4–8.3)	1.45 (1.09–1.92)	**.010**
Ischemic stroke				
High education	16/356	1.2 (.7–1.9)	Ref.	Ref.
Medium education	36/947	1.0 (.7–1.4)	.94 (.50–1.75)	.835
Low education	32/992	1.0 (.7–1.4)	.85 (.45–1.60)	.616
Intracerebral haemorrhage				
High education	3/356	.2 (.0–.6)	Ref.	Ref.
Medium education	1/947	.0 (.0–.2)	.23 (.02–2.67)	.238
Low education	3/992	.1 (.0–.3)	.60 (.10–3.75)	.583

*Note*: Significant p-values are shown in bold.

Abbreviations: aHR, adjusted Hazard Ratio, CI, confidence interval, IR, incidence rate.

observed also for the medium educational level group (aHR: 1.20, 95%CI: .93–1.55).

When analysing the individual components of the primary outcome, we found similar results for the risk of all-cause mortality, with low educational level groups showing an increased risk compared to the high educational level (aHR: 1.45, 95%CI: 1.09–1.92). No statistically significant differences were observed for the risk of IS and ICH (Table 2).

4 | DISCUSSION

In this analysis from the WARCEF trial, our main results are as follows: (i) low educational level was common in our cohort of HFrEF patients, and was associated with female sex, marital status, tabagism and specific ethnic subgroups; (ii) compared to patients with high educational level, those with low education showed worse prognosis (as encompassed by higher risk for the
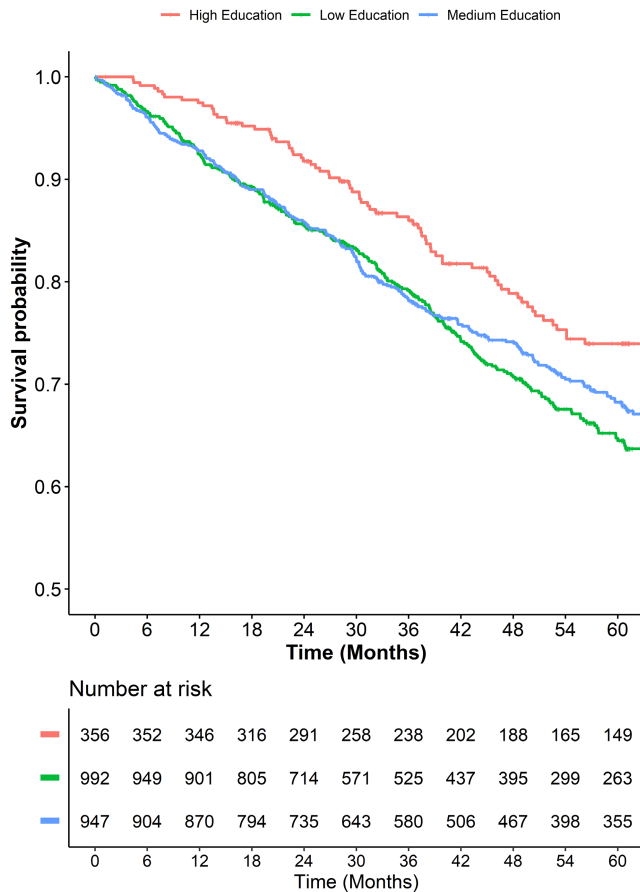
FIGURE 1 Kaplan–Meier curves for the risk of the primary composite outcome according to educational level. Log-rank *p*, high versus low education = .007; high versus medium education = .055; medium versus low education = .32.

primary composite outcome of all-cause death, as well as the composite outcome of death, IS and ICH, and for all-cause death when considered as an exploratory secondary outcome); (iii) no statistically significant differences were observed for the other, non-fatal secondary outcomes, which incidences were found similar (and low) between groups.

The increasing awareness on the importance of SDOH in patients with HF have led to a growing interest in the potential influence of these non-traditional risk factors on the prognosis of these patients.[17] While previous studies have reported an association between low educational status and poor prognosis in HF patients,[18] there is still high uncertainty on the extent of this association in subjects with HFrEF.

In this study, using data from the WARCEF trial, including 2295 patients with HFrEF and complete data on educational status, we showed how, compared with patients with high level of education, those with low education level had a higher risk of the primary composite outcome of all-cause death, IS and ICH. We also observed a similar trend, although non-significant and with lower

magnitude, for patients with medium educational level (i.e., those high school graduated and who did not complete college). On the other side, we did not find differences for patients with medium versus low educational level, as well as when considering the other secondary, non-fatal outcomes. These results may have been influenced by the relatively low incidence of such events in this cohort.

Our findings are consistent with several studies which focused on HF,[13,14,19] and further expand the evidence on the association between educational status and the risk of major outcomes in patients with HF. Indeed, our findings suggest that risk may be continuous across the education level, with lower risk in highly educated patients, and less differences between those with medium versus low educational levels. These results were also observed when analysing all-cause death as an individual component of the primary outcome, and suggest that patients with high educational level had an overall better prognosis in our cohort. Although other observational studies observed similar distribution of educational levels in HFrEF patients and similar effect on their prognosis when stratifying for the educational levels,[13,14,19] our analysis derives from a randomized controlled trial where an independent endpoint adjudication committee evaluated adverse clinical outcome, moreover, compared to observational retrospective data, in our cohort, the presence of other high quality data on other SDOH, beside educational status, as marital status, or social background, which are only rarely explored in HFrEF patients, increase the granularity of cohort examined. Notably, patients enrolled were mostly treated according to guideline-directed medical therapy available at the time of the trial, basically composed by angiotensin converting enzyme inhibitor or angiotensin receptor blockers, mineral receptor antagonists, and an evidence-based beta-blocker. Although some differences were observed between groups, the overall high use of such drugs represent a strength point of our analysis, and particularly on the association between educational level and risk of the primary outcome. Moreover, as reported by a recent comprehensive meta-analysis,[20] the major issue arises in the lack of reporting SDOH variables, and a substantial knowledge gap exists in understanding how SDOH influence the outcomes of patients with HF, therefore it is important to reduce the knowledge gap with data coming from clinical trials.

Reasons for worse prognosis in HFrEF patients with low educational status could be explained by the clustering of other low socioeconomic indicators, all exerting a detrimental effect on prognosis of patients with HFrEF. Indeed, low educational level is associated with low income and unemployment,[21] which could increase the lack

of health insurance and hence lower access to healthcare, especially in countries with private healthcare services.[21]

Moreover, the association between low education level and other risk factors may contribute to explain our findings. In this analysis, low educational level was associated with the highest prevalence of active smoking, and this could further reinforce the hypothesis that unhealthy lifestyles (including unhealthy diet and/or sedentary lifestyle) may modulate the relationship between educational level and worse prognosis.[22,23] Moreover, low educational level might reflect a gap in healthcare literacy and lack of awareness of healthcare problems and risk of adverse events: indeed, a high proportion of HF patients with low health literacy has been estimated (up to 39%),[24] where ethnicity and years of education were found to be predictive factors.[24] Unsurprisingly, high health literacy was associated with a reduced risk of death and cardiovascular mortality[25] while a lower health literacy was associated with poor reading and understanding of instruction for dosing and identification of medications,[26,27] with a strong impact on the adherence and ultimately the beneficial effect of the treatment prescribed.[28,29] Given this evidence, intervention on modifiable socioeconomic indicators, such as teaching how to deal with the medical conditions and drugs prescribed, should be implemented, in order to improve health literacy levels and ultimately improve prognosis of these patients.[30,31] Of note, most of the interventions explored to date has been directed on health education, but only few of these explored the benefit of a health education programme on the overall survival, with inconsistent results.[32,33]

In addition, as previously reported in this cohort,[34] low educational status has been shown to be a predictor of cognitive decline over time. Moreover, the presence of cognitive impairment at baseline has been associated with worse outcomes in HF patients.[35] This interplay highlights the importance of considering low educational levels in patients with HF, in order to improve their overall prognosis.

Future studies on this population should implement the evaluation of SDOH along with other, measurable, variables as the number of concomitant comorbidities as well as the presence of polypharmacy in order to tailor interventions and treatment to each single patient.

Our results on secondary outcomes did not show statistically significant differences in the risk of non-fatal outcomes such as IS and ICH across the educational level groups. While these results may suggest that educational status may have an unspecific effect on the overall prognosis of patients with HFrEF, it should be noted that these analyses were performed considering the non-fatal events occurring as first-events of the trial's primary endpoints, and that—overall—incidence rates for

these events were low in this cohort. As such, these results should be interpreted with caution and regarded as hypothesis-generating.

Taken together, our results have several clinical implications. First, acknowledging the impact of SDOH on the prognosis of patients with HFrEF (and, more generally, on patients with chronic cardiovascular diseases) is important to identify those individuals with non-traditional risk factors that may present a residual risk of adverse events, regardless of the therapeutic efforts made to improve their prognosis. In this regard, we clearly need more evidence exploring the interplay between SDOH and the risk of major outcomes in these patients. Our analysis, indeed, provide useful insights on this issue, underlying the role of educational level on the natural history of HFrEF patients, and therefore identifying a subgroup of patients who may needs specific intervention, which can take into account their unmet needs of health, to improve prognosis. While more efforts should be produced to evaluate the association between SDOH and prognosis in HFrEF patients, our analysis show that accounting for such factors in the comprehensive management of these patients may have a key role in improving our care approaches. How we can implement a routine-based evaluation and management of such non-traditional risk factors remains unclear and currently represent a key area of development in the context of HFrEF and, more generally, cardiovascular diseases.

4.1 | Strengths and limitations

This analysis is based on a cohort of well-characterized HFrEF patients, recruited in an RCT; moreover, our definition of educational level relies on the use of school qualification, thus providing a reproducible and reliable categorization of patients. Finally, almost all patients originally included in the trial had data available on educational level, thus contributing to strengthen our results.

Nonetheless, we acknowledge some limitations. First, this is a non-prespecified post-hoc analysis of a RCT, thus not being specifically powered for detecting differences in the risk of the primary outcome according to the educational level. We considered educational level as reported in the case report form by the investigators, thus being not externally certified. We were also unable to explore potential subgroups differences due to reduced power of such analysis, and further studies are therefore needed to understand whether educational level can exert a different prognostic effect in specific categories of patients, including older patients. Moreover, although we tried to adjust our regression models for several potential confounders, we cannot exclude the contribution of other,

unaccounted confounders in the results observed, including other SDOH, such as income, that may be associated with low educational level and were not recorded in this trial. Additionally, data on other diseases, and particularly non-cardiovascular conditions such as sleep apnoea and chronic obstructive pulmonary disease, were not available for analysis; we therefore cannot exclude the contribution of these conditions (which are linked with the pathophysiology of HF and its outcomes[36,37]) as potential confounders on the association between educational level and outcomes. Similarly, other variables, such as the degree of congestion at baseline, may have contributed to the results observed; nonetheless, we believe that such influence is unlikely to be significant, also considering the other variables included in our regression model, including NYHA class. As no data on compliance to medication were available, we also cannot account whether the adherence to medications stratified by educational levels could have influenced our results.

Moreover, when the WARCEF trial was performed, some of the current treatments for HF (including Sodium-Glucose Transport Protein 2 inhibitors, Angiotensin Receptor-Neprilysin Inhibitors, vericiguat and others) were not yet available; further studies, including more recent cohort of HFrEF patients, are therefore needed to confirm these results. Nonetheless, this clinical trial cohort has adjudicated outcomes which is a strength of this analysis. Finally, we focused our analysis on the trial's primary composite outcome, using a time-to-first-event approach; consistently, we explored the individual components of such composite endpoint as secondary outcomes, observing low rates for non-fatal events. Apart from being influenced by the potential competing risk of death, this could have led to low power for such exploratory analysis, and therefore the results should be interpreted with caution and as hypothesis generating.

5 | CONCLUSIONS

In this post-hoc analysis of the WARCEF trial, HFrEF patients with low educational level showed worse prognosis compared to those with high educational status, with increased risk of the composite outcome of IS, ICH, or death from any cause at follow-up. Integration of educational level and other SDOH in the risk stratification and management of HFrEF is important to improve prognosis of these patients.

AUTHOR CONTRIBUTION

Bernadette Corica, Giulio Francesco Romiti, Marco Proietti and Gregory Y.H. Lip conceived and design the analysis. Bernadette Corica and Giulio Francesco Romiti analysed the data, Bernadette Corica, Giulio Francesco Romiti and Amalie Helme Simoni interpreted the data and drafted the manuscript. Gregory Y.H. Lip, Marco Proietti, Davide Antonio Mei, Tommaso Bucci, John L.P. Thompson, Min Qian and Shunichi Homma revised the manuscript and gave relevant intellectual contributions. All authors read and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

Giulio Francesco Romiti reports consultancy for Boehringer Ingelheim and an educational grant from Anthos, outside the submitted work. No fees are directly received personally. Marco Proietti is investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. Gregory Y.H. Lip has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo and Anthos. No fees are received personally. Gregory Y.H. Lip is a NIHR Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871. All other authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request, and after approval of all other co-investigators.

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How to cite this article: Corica B, Romiti GF, Simoni AH, et al. Educational status affects prognosis of patients with heart failure with reduced ejection fraction: A post-hoc analysis from the WARCEF trial. *Eur J Clin Invest*. 2024;00:e14152. doi:10.1111/eci.14152