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a nationwide study

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CLINICAL RESEARCH

Long-term cardiovascular outcomes among immigrants and non-immigrants in cardiac resynchronization therapy: a nationwide study

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Aims To date, potential differences in outcomes for immigrants and non-immigrants with a cardiac resynchronization therapy (CRT), in a European setting, remain underutilized and unknown. Hence, we examined the efficacy of CRT measured by heart failure (HF)-related hospitalizations and all-cause mortality among immigrants and non-immigrants.

Methods and results All immigrants and non-immigrants who underwent first-time CRT implantation in Denmark (2000–2017) were identified from nationwide registries and followed for up to 5 years. Differences in HF related hospitalizations and all-cause mortality were evaluated by Cox regression analyses. From 2000 to 2017, 369 of 10 741 (3.4%) immigrants compared with 7855 of 223 509 (3.5%) non-immigrants with a HF diagnosis underwent CRT implantation. The origins of the immigrants were Europe (61.2%), Middle East (20.1%), Asia-Pacific (11.9%), Africa (3.5%), and America (3.3%). We found similar high uptake of HF guideline-directed pharmacotherapy before and after CRT and a consistent reduction in HF-related hospitalizations the year before vs. the year after CRT (61% vs. 39% for immigrants and 57% vs. 35% for non-immigrants). No overall difference in 5-year mortality among immigrants and non-immigrants was seen after CRT [24.1% and 25.8%, respectively, *P*-value = 0.50, hazard ratio (HR) = 1.2, 95% confidence interval (CI): 0.8–1.7]. However, immigrants of Middle Eastern origin had a higher mortality rate (HR = 2.2, 95% CI: 1.2–4.1) compared with non-immigrants. Cardiovascular causes were responsible for the majority of deaths irrespective of immigration status (56.7% and 63.9%, respectively).

Conclusion No overall differences in efficacy of CRT in improving outcomes between immigrants and non-immigrants were identified. Although numbers were low, a higher mortality rate among immigrants of Middle Eastern origin was identified compared with non-immigrants.

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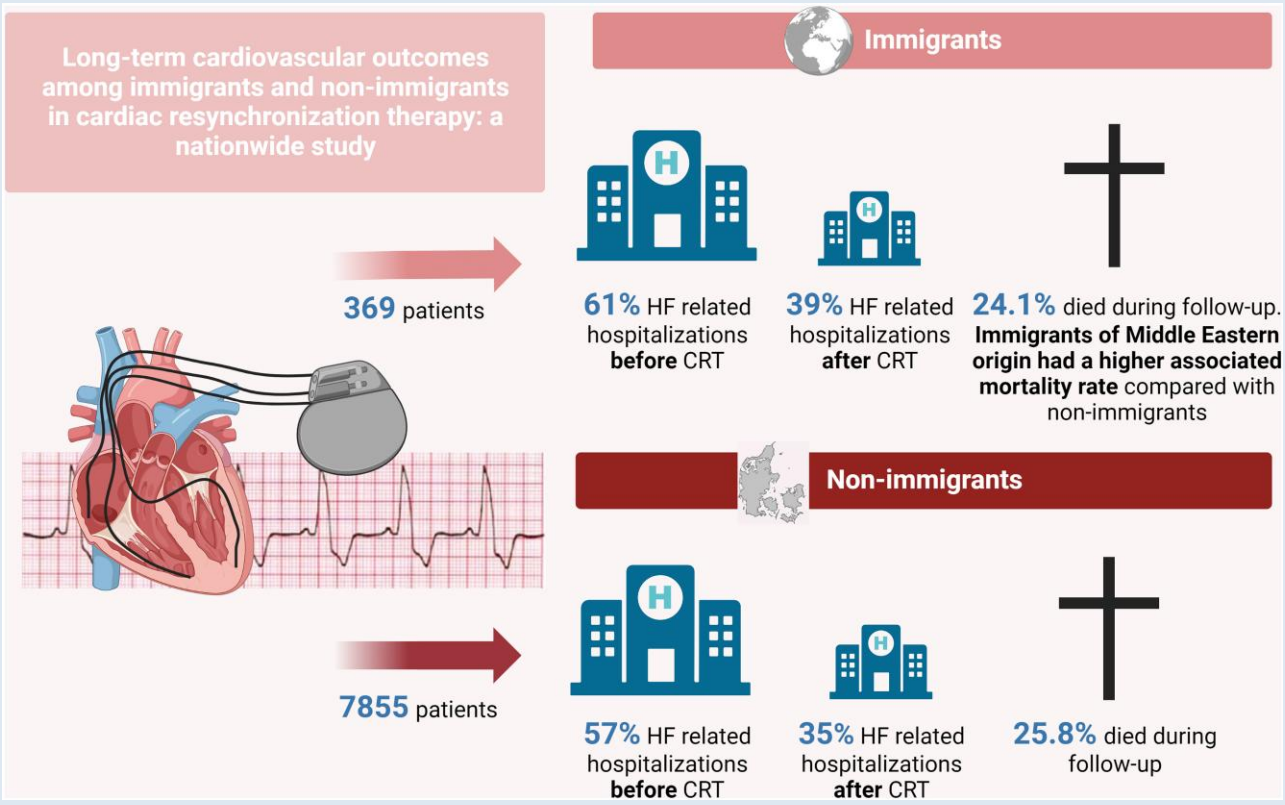
Graphical Abstract



Keywords CRT • Epidemiology • Ethnicity • Heart failure • Mortality

What's new?

- Accessing differences in heart failure-related hospitalizations and long-term mortality between immigrants and non-immigrants after cardiac resynchronization therapy (CRT) in a European setting, which has been sparsely described previously.
- Long-term mortality after CRT was not affected by immigration status as this was equal for immigrants and non-immigrants.
- A significant and similar reduction in heart failure-related hospitalizations was observed for both immigrants and non-immigrants when comparing the year before with the year after CRT implantation.

Introduction

In 2017, the Danish population consisted of 591 438 immigrants and 5 157 331 non-immigrants.[1] Immigrants are exposed to different health risks before, during, and after immigration and may face several barriers to healthcare services, which in combination might lead to adverse cardiovascular outcomes compared with their non-immigrant counterparts.[2,3,4]

In general, cardiac resynchronization therapy (CRT) significantly improves quality of life (e.g. measured by fewer heart failure-related hospitalizations) and overall survival in patients with symptomatic heart failure (despite optimal pharmacotherapy), reduced left ventricular ejection fraction (LVEF), and a QRS-duration ≥130 ms (previously ≥120 ms).[5] However, the response to CRT may not be uniform with these parameters, and the beneficial effect may hence vary between immigrants and non-immigrants. Social determinants (e.g. socioeconomics) and health can have a disproportionate impact on immigrants compared to nonimmigrants.[6]

To date, only few studies have examined disparities in implantation rates and outcomes after CRT between immigrants and non-immigrants. A study by Ziaeian *et al.*[7] found no significant difference between race/ethnicity and the clinical effectiveness, shown as 24-month survival, after either implantable cardioverter defibrillator (ICD) or CRT implantation. Moreover, the majority of studies performed are predominantly from North American cohorts which may affect the clinical applicability to other healthcare settings. Also, the previous studies mainly focused on the patient selection for CRT and long-term cardiovascular outcomes for immigrants who underwent CRT remain underutilized.[8]

In this nationwide study, we sought to identify differences in implantation rate, heart failure-related hospitalizations, and long-term all-cause mortality, including cause-specific mortality, from a real-life, unselected nationwide cohort of immigrants and non-immigrants who received a CRT [i.e. CRT-pacemaker (CRT-P) or a CRT-defibrillator (CRT-D)].

Methods

Registries

A unique and permanent identification number is assigned to all Danish citizens through the Civil Registration System enabling cross-linkage, on an individual level, among the nationwide registries. Several registries were used in this study including the Danish Pacemaker and ICD Register, established in 1982, which is a clinical database comprising information on pacemaker and ICD implantations performed in Denmark. All device implantations

(e.g. CRT) in Denmark are performed in public hospitals ensuring equal treatment modalities. Information in the clinical registry includes information on time of device implantation, implant indication, device type, lead type, New York Heart Association (NYHA) functional class, LVEF, symptomology, and information from follow-up (i.e. appropriate/inappropriate device therapy, device-related complications, generator replacements, system upgrades/downgrades, and revisions). The Danish National Population Statistics Register holds information on births, deaths, emigration, marital status, divorces, and highest completed education.[9] The Danish National Patient Registry holds information on all hospital admissions since 1978. Each hospital admission and hospital discharge are registered with a primary diagnosis, one or two secondary diagnoses if appropriate, and classified according to the International Classification of Diseases 10 (ICD-10) since 1994.[10] The Danish National Prescription Registry holds information on all pharmacotherapy prescriptions from Danish pharmacies since 1995 which are recorded using the Anatomical Therapeutic Chemical (ATC) system. Because the Danish government health care system ensures unrestricted access to healthcare and partial reimbursement for claimed pharmacotherapy, all pharmacies are by law required to disclose all dispensed prescriptions making the register both valid and accurate.[11] The National Causes of Death Registry contains information on time of death, primary cause of death, and if appropriate, contributing causes of death.[12]

Immigration status

In Denmark, all foreign citizens, staying more than 3 months, are required to achieve a residence permit. Information on country of origin, date of immigration, date of emigration, and descendants of immigrants is registered in the Danish National Population Statistics Register where immigration status is classified, according to statistics Denmark, as:

- Danish origin: a person is designated as having Danish origin if at least one parent has Danish citizenship and are born in Denmark, regardless of the person's place of birth.
- Immigrant: persons who are born outside Denmark where both parents are born outside Denmark and do not have Danish citizenships.
- Descendants of immigrants: persons who are born in Denmark and where both parents are born outside Denmark and do not have Danish citizenships.

Importantly, in this study, patients of Danish origin and descendants of immigrants were grouped together as non-immigrants. This was done in accordance with our previous study which found that descendants of immigrants had similar baseline characteristics as non-immigrants.[13] Morevoer, immigrants were grouped together according to region of origin (i.e. Africa, America, Europe, Asia-Pacific, and Midlle-East). Notably, South- and North-America were grouped together to avoid reporting of low case numbers.

Study population

The present study included all patients ≥18 years of age who underwent a first-time CRT implantation (i.e. CRT-D or CRT-P) according to the Danish Pacemaker and ICD Register between 1 January 2000 and 31 December 2017. Importantly, all patients were eligible for at least 1 year of follow-up after CRT implantation.

Pharmacotherapy, comorbidity, and education

Concomitant pharmacotherapy was identified using ATC codes from the National Prescription Registry and defined as a claimed prescription ≤90 days before CRT implantation (see Supplementary material online, *Appendix* for details).

Information on patient comorbidity was obtained using hospital discharge diagnoses ≤10 years before CRT implantation from the Danish National Patient Register (see Supplementary material online, *Appendix* for details).[14] Heart failure related-hospitalizations were identified 1 year before and 1 year after CRT implantation (ICD-10: I42, I50, J819, I110, I130, and I132) as primary or secondary diagnose. The heart failure diagnosis (ICD-10: I50) has previously been found to have a positive predictive value of 95%.[15]

Information on highest achieved education according to the International Standard Classification of Education (ISCED) was identified. Education level was further grouped as: basic school (ISCED 0–2), high school or vocational education (ISCED 3), and higher education (ISCED 5–8), as done previously.[16]

Study outcomes

The primary study outcome was all-cause mortality after CRT implantation for immigrants and non-immigrants. Secondary study outcomes were implantation rate and heart failure related hospitalizations 1 year before compared with 1 year after CRT implantation and cause-specific mortality for immigrants and non-immigrants.

Statistical analyses

Continuous variables were compared and tested using the Kruskal–Wallis test, whereas categorical variables were compared and tested using the χ^2 test. Difference in the incidence of all-cause mortality between immigrants and non-immigrants was estimated using a cumulative incidence curve. Descriptive data were reported as proportions of heart failure-related hospitalizations 1 year before compared with 1 year after CRT implantation. Differences in outcomes were calculated using the χ^2 test. Tests for differences between the curves were performed by the log-rank test.

Multivariable Cox regression was performed to determine risk factors associated with heart failure-related hospitalizations and all-cause mortality. The models were adjusted for factors of clinical relevance for the outcome: sex, 5-year increment in age, year of CRT implantation, CRT type (i.e. CRT-P and CRT-D), QRS-duration, LVEF, NYHA functional class, immigration status (i.e. immigrants and non-immigrants) or region of origin (i.e. Africa, America, Asia-Pacific, Europe, and Middle East), smoking, body mass index, income (quartiles), marital status, ischaemic heart disease, atrial fibrillation, cancer, angiotensin-converting enzyme inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. Education level was not included in the primary adjusted model but was added in a sensitivity analysis, due to collinearity between origin and education level, also done previously.[13] Moreover, several studies have found income level to be a better indicator for socioeconomic status than education level.[17,18] No clinical meaningful interaction was found when interaction between age and sex was tested for.

Danish law prohibits reporting of low group numbers ($n \leq 3$). Thus, low group numbers have been replaced with '≤3' throughout the manuscript. The exact numbers are known to the investigators.

All statistical analyses were performed using either SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) or R Core Team (2020) version 4.0.3. A two-sided *P*-value <0.05 was considered statistically significant.

Ethics

The study was approved by the Danish Data Protection Agency (*P*-2019–400). Registry-based analyses using de-identifiable data do not need an ethics approval in Denmark.

Results

Patient characteristics

Overall, 369 of 10 741 (3.4%) immigrants with a heart failure diagnosis compared with 7855 of 223 509 (3.5%) non-immigrants with a heart failure diagnosis underwent CRT implantation between 2000 and 2017 in Denmark. Moreover, in this period, approximately 369 of 591 438 (0.06%) of immigrants compared with 7855 of 5 157 331 (0.15%) non-immigrants from the entire Danish population underwent CRT implantation.[1] Of the 369 immigrants with a CRT, 61.2% originated from Europe, 20.1% the Middle East, 11.9% Asia-Pacific, 3.5% Africa, and 3.3% USA. Median time from first immigration day to CRT implantation was 23 years [interquartile range (IQR): 15–32 years].

A similar proportion of the immigrants and non-immigrants were in treatment with ACE-inhibitors (88.3% vs. 89.1%), beta-blockers (80.5% vs. 81.5%), and mineralocorticoid receptor antagonists (54.2% vs.

Table 1 Patient characteristics for immigrants and non-immigrants in cardiac resynchronization therapy

	Immigrants ($n = 369$)	Danish born ($n = 7855$)	*P*-value	Total ($n = 8224$)
Sex (male), *n (%)*	300 (81.3)	6152 (78.3)	0.19	6452 (78.5)
Age at CRT implantation, *[years, median (Q1, Q3)]*	67 (58, 74)	70 (62, 76)	<0.001	70 (62, 76)
CRT-D, *n (%)*	229 (62.1)	4273 (54.4)	0.005	4502 (54.7)
Left ventricular ejection fraction *(%, median [Q1, Q3])*	25 (20, 30)	25 (20, 30)	0.01	25 (20, 30)
QRS duration, *(ms, median [Q1, Q3])*	160 (140, 170)	160 (140.0, 173.8)	0.66	160 (140, 173)
NYHA, *median (Q1, Q3)*	3 (2, 3)	3 (2, 3)	0.09	3 (2, 3)
Lifestyle risk factors and socioeconomic status, *n* (%)				
Body mass index, *kg/m^2, median (Q1, Q3)*	27.1 (23.9, 30.1)	26.5 (23.9, 29.9)	0.33	26.5 (23.9, 30.0)
Current/previous smoker	109 (62.3)	2478 (64.0)	0.70	2587 (64.0)
Basic school	98 (33.0)	3035 (39.5)	—	3133 (39.2)
High school or vocational education	112 (37.7)	3372 (43.8)	—	3484 (43.6)
Higher education	87 (29.3)	1283 (16.7)	<0.001	1370 (17.2)
Living alone	79 (21.4)	1849 (23.5)	0.38	1928 (23.4)
Comorbidities <10 years before CRT implantation, *n* (%)				
Chronic heart failure	349 (94.6)	7361 (93.7)	0.57	7710 (93.8)
Ischaemic heart disease	270 (73.2)	5249 (66.8)	0.01	5519 (67.1)
Atrial fibrillation	122 (33.1)	3024 (38.5)	0.04	3146 (38.3)
Hypertension	317 (85.9)	7041 (89.6)	0.03	7358 (89.5)
Diabetes	255 (69.1)	5203 (66.2)	0.28	5458 (66.4)
Chronic obstructive pulmonary disease	51 (13.8)	1090 (13.9)	1	1141 (13.9)
Cancer	28 (7.6)	728 (9.3)	0.32	756 (9.2)
Chronic renal failure	37 (10.0)	825 (10.5)	0.84	862 (10.5)
Pharmacotherapy <90 days before CRT implantation, *n* (%)				
Angiotensin-converting enzyme inhibitors	265 (71.8)	5917 (75.3)	0.14	6182 (75.2)
Beta-blockers	241 (65.3)	5464 (69.6)	0.09	5705 (69.4)
Mineralocorticoid receptor antagonists	144 (39.0)	2930 (37.3)	0.54	3074 (37.4)
Diuretics	253 (68.6)	5634 (71.7)	0.21	5887 (71.6)
Anti-platelets	235 (63.7)	5246 (66.8)	0.24	5481 (66.6)
Anti-depressants	42 (11.4)	813 (10.4)	0.58	855 (10.4)

CRT-D, cardiac resynchronization therapy-defibrillator; ms, millisecond; NYHA, New York Heart Association.

52.6%) within the year before CRT implantation. This similarity was consistent in the year following CRT implantation for ACE-inhibitors (82.4% vs. 83.6%), beta-blockers (83.2% vs. 84.3%), and mineralocorticoid receptor antagonists (55.8% vs. 55.6%) for immigrants and non-immigrants, respectively.

Furthermore, no significant difference in LVEF, NYHA functional class, and/or QRS-duration was observed between immigrants and non-immigrants at time of CRT implantation. Overall, the immigrant population was younger [67 years (IQR: 58–74 years) vs. 70 years (62–76 years), *P*-value < 0.001], more likely to have completed a higher education, and more often had a history of ischaemic heart disease (73.2% vs. 66.8%, *P*-value = 0.013). Patient characteristics for immigrants and non-immigrants are listed in *Table 1*.

In general, patients from Europe and America were more likely to have completed a higher education compared with patients from the Middle East and Asia-Pacific. No other significant differences in patient characteristics across region of origins were observed (including age at CRT implantation, burden of comorbidities, LVEF, NYHA functional class, and QRS-duration). Patient characteristics for immigrants according to region of origin are listed in *Table 2*.

All-cause mortality after cardiac resynchronization therapy

During a median follow-up of 3.7 years (IQR: 2.0–5.0 years) for the immigrants and 3.7 years (IQR: 1.9–5.0 years) for the non-immigrants, 24.1% from the immigrant population died (median age at time of death was 72 years, IQR: 64–79 years) compared with 25.8% of the non-immigrants (median age at time of death was 75 years, IQR: 68–81 years). Median time to death after CRT implantation was 787 days (IQR: 267–1251 days) for immigrants and 691 days (IQR: 298–1185 days) for non-immigrants (*P*-value 0.78). Depicted in *Figure 1* is a cumulative incidence curve for time to all-cause mortality. The figure shows similar cumulative incidences for all-cause mortality between immigrants and non-immigrants during up to 5 years of follow-up (31% and 32%, respectively, $P = 0.5$). For both immigrants and non-immigrants, cardiovascular causes were responsible for the majority of deaths (56.7% and 63.9%, respectively) (*Figure 2*). Moreover, other frequent causes of death for non-immigrants were cancer (13.2%) and respiratory causes (5.4%), whereas death from other causes (18.9%) (including psychiatric disease-related causes) and endocrine causes (8.9%) were more common among immigrants.

Table 2 Patient characteristics for immigrants in cardiac resynchronization therapy stratified by region of origin.

	Africa ($n = 13$)	America ($n = 12$)	Asia-Pacific ($n = 44$)	Europe ($n = 226$)	Middle East ($n = 74$)	*P*-value
Sex (male), *n* (%)	≥10 (≥77.0)	≥9 (≥75.0)	31 (70.5)	188 (83.2)	59 (79.7)	0.29
Age at CRT implantation, *years, median (Q1, Q3)*	65 (59, 67)	68.5 (56, 77)	68 (59, 73)	69 (59, 75)	61 (57, 71)	0.16
CRT-D, *n* (%)	9 (69.2)	8 (66.7)	26 (59.1)	141 (62.4)	45 (60.8)	0.96
Left ventricular ejection fraction, *%, median (Q1, Q3)*	20 (20, 26)	25 (18, 25)	25 (20, 30)	25 (20, 30)	25 (20, 30)	0.72
QRS duration, *ms, median (Q1, Q3)*	160 (148, 163)	160 (139, 180)	150 (130, 166)	160 (143, 172)	158 (141, 170)	0.57
NYHA, *median (Q1, Q3)*	3 (2, 3)	2 (2, 3)	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.27
Lifestyle risk factors and socioeconomic status, *n* (%)						
Body mass index (kg/m^2), *median (Q1, Q3)*	28.9 (23, 31)	28.1 (27, 30)	25.1 (22, 30)	27.2 (24, 30)	26.5 (23, 29)	0.95
Current/previous smoker	4 (80.0)	4 (100.0)	8 (33.3)	72 (66.7)	21 (61.8)	0.01
Basic school	≤3	≤3	20 (55.6)	44 (23.9)	28 (50.0)	—
High school or vocational education	6 (60.0)	4 (36.4)	9 (25.0)	76 (41.3)	17 (30.4)	—
Higher education	≤3	4 (36.4)	7 (19.4)	64 (34.8)	11 (19.6)	0.001
Living alone	≤3	≤3	9 (20.5)	49 (21.7)	16 (21.6)	0.99
Comorbidities ≤10 years before CRT implantation, *n* (%)						
Chronic heart failure	≥10 (≥77.0)	≥9 (≥75.0)	40 (90.9)	215 (95.1)	70 (94.6)	0.69
Ischaemic heart disease	9 (69.2)	9 (75.0)	31 (70.5)	162 (71.7)	59 (79.7)	0.71
Atrial fibrillation	5 (38.5)	4 (33.3)	10 (22.7)	83 (36.7)	20 (27.0)	0.30
Hypertension	≥10 (≥77.0)	8 (66.7)	39 (88.6)	194 (85.8)	64 (86.5)	0.35
Diabetes	≥10 (≥77.0)	7 (58.3)	32 (72.7)	151 (66.8)	55 (74.3)	0.60
Chronic obstructive pulmonary disease	≥10 (≥77.0)	≥9 (≥75.0)	39 (88.6)	198 (87.6)	59 (79.7)	0.47
Cancer	0 (0.0)	≤3	≤3	20 (8.8)	≤3	0.36
Chronic renal failure	≤3	≤3	5 (11.4)	20 (8.8)	9 (12.2)	0.88
Pharmacotherapy ≤90 days before CRT implantation, *n* (%)						
Angiotensin-converting enzyme inhibitors	8 (61.5)	6 (50.0)	29 (65.9)	175 (77.4)	47 (63.5)	0.04
Beta-blockers	6 (46.2)	8 (66.7)	26 (59.1)	152 (67.3)	49 (66.2)	0.51
Mineralocorticoid receptor antagonists	≤3	≤3	21 (47.7)	88 (38.9)	30 (40.5)	0.24
Diuretics	8 (61.5)	8 (66.7)	30 (68.2)	156 (69.0)	51 (68.9)	0.99
Anti-platelets	5 (38.5)	7 (58.3)	27 (61.4)	154 (68.1)	42 (56.8)	0.12
Anti-depressants	≤3	≤3	≤3	30 (13.3)	7 (9.5)	0.69

CRT-D, cardiac resynchronization therapy-defibrillator; ms, millisecond; NYHA, New York Heart Association.

Risk factors associated with all-cause mortality after cardiac resynchronization therapy

In the multivariable Cox regression analysis on risk factors for all-cause mortality, being an immigrant was not identified as a significant risk factor for all-cause mortality compared with non-immigrants [hazard ratio (HR) = 1.2, 95% confidence interval (CI): 0.9–1.7] (*Figure 3*). In a sub-analysis we grouped immigrants and descendants together and compared them with non-immigrants (supplemental *Figure 1*). The sub-analysis yielded similar results as the main analysis depicted in *Figure 3*.

Middle Eastern origin (HR = 2.2, 95% CI: 1.2–4.1) was found as a significant risk factor for all-cause mortality compared with non-immigrants (*Figure 4*). Also, male sex (HR = 1.7, 95% CI: 1.4–2.1) and atrial fibrillation (HR = 1.2, 95% CI: 1.1–1.4) were all significantly associated with all-cause mortality. Moreover, a graded effect between NYHA functional class and all-cause mortality was observed (i.e. a high NYHA functional class was associated with all-cause mortality). Use of ACE-inhibitors was associated with reduced likelihood of mortality (HR = 0.7, 95% CI: 0.6–0.8) as was overweight/obesity (i.e. compared with normal weight) (HR = 0.7, 95% CI: 0.6–0.9) and high-income class (HR = 0.7, 95% CI: 0.6–0.8) (see Supplementary material online, *Figure S2*). However, when we additionally adjusted for education level, Middle Eastern origin was no longer associated with all-cause mortality, although it showed a similar trend as in the main analysis (HR = 1.8, 95% CI: 0.8–3.8) (*Figure 4*). Instead, higher education (HR = 0.8, 95% CI: 0.6–0.99) was found to have a protective effect against all-cause mortality as well as living alone (HR = 1.4, 95% CI: 1.2–1.6) was significantly associated with all-cause mortality (see Supplementary material online, supplemental *figure S3*).

Heart failure-related hospitalizations

The proportion of patients who had at least one heart failure related hospitalization 1 year before compared with 1 year after CRT implantation were similar for immigrants and non-immigrants; this included a consistent and significant reduction in heart failure-related hospitalizations for immigrants (before CRT implantation: 61% vs. after CRT implantation: 39%, *P*-value < 0.001) and non-immigrants (before CRT

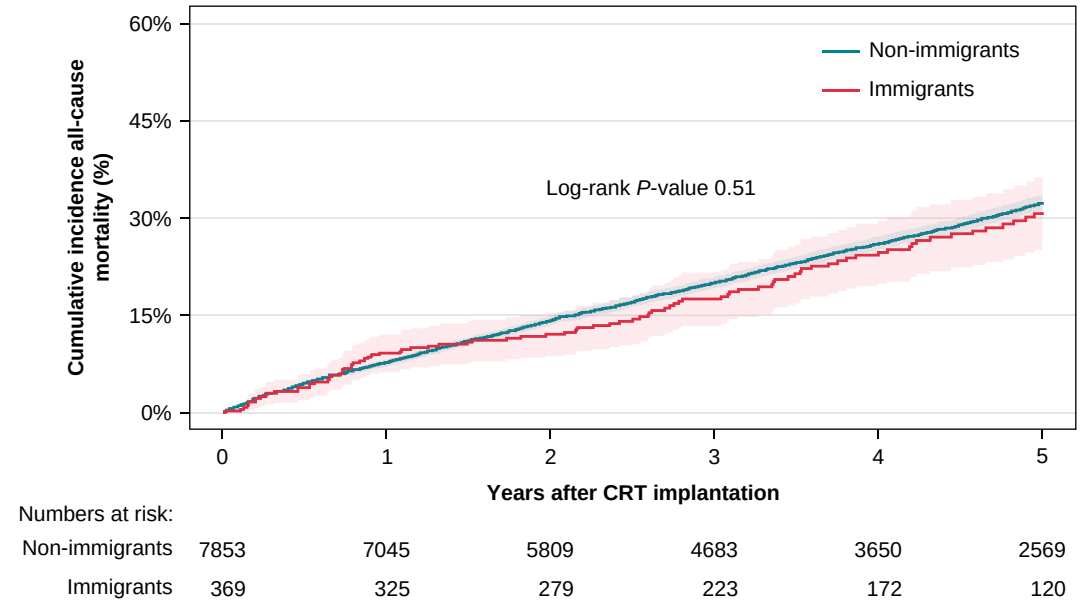


Figure 1 Cumulative incidence curve on all-cause mortality for immigrants compared with non-immigrants in cardiac resynchronization therapy. CRT, cardiac resynchronization therapy.

implantation: 57% vs. after CRT implantation: 35%, *P*-value < 0.001). Moreover, in the multivariable Cox regression analysis on risk factors for heart failure-related hospitalizations 1 year after CRT implantation, being an immigrant was not identified as a significant risk factor compared with non-immigrants (HR = 1.2, 95% CI: 0.9–1.6) (see Supplementary material online, *Figure S4*).

Discussion

This nationwide study on cardiovascular outcomes after first time CRT implantation according to immigration status had three principal findings. First, CRT implantation rate was not affected by immigration status as this was equal for immigrants and non-immigrants, as well as a significant and similar reduction in heart failure-related hospitalizations was observed for both immigrants and non-immigrants when comparing the year before CRT implantation with the year after CRT implantation. Second, no difference in all-cause mortality between immigrants of all origins and non-immigrants was observed during a 5-year follow-up period after implantation of a CRT. Moreover, among patients who died during follow-up, cardiovascular-related causes were responsible for the majority of deaths for both immigrants and non-immigrants. Third, compared with non-immigrants, Middle Eastern origin was associated with all-cause mortality.

The beneficial effects of CRT are well-established in patients with symptomatic heart failure. However, while previous studies mainly focused on response to CRT and post-implant care, including methods to optimize electrical and mechanical synchrony, few studies have examined differences in cardiovascular outcomes between immigrants and non-immigrants after CRT implantation. In general, immigrants and their descendants constitute a progressively larger proportion of the Danish population (~14%), and in 2021, the Danish population consisted of 260.304 immigrants from Western countries and 357.466 immigrants from non-western countries.[1] Although, fewer immigrants from the general population underwent CRT implantation compared with non-immigrants (0.06% and 0.15%, respectively), a similar proportion of immigrants and non-immigrants with a heart failure diagnosis received a CRT between 2000 and 2017 (3.47% and 3.51%, respectively).[1] The difference in CRT implantation rates between immigrants is most likely multiple and information on pharmacotherapy compliance as well as heart failure related factors should be assessed for all patients with heart failure to evaluate if immigrants with heart failure are offered a CRT on an equal basis if they are eligible for one according to current guidelines.

Even though access to the healthcare system is, roughly, equal for all Danish citizens, immigrants may still encounter a broad spectrum of obstacles. First, a recent study by Januszkiewicz *et al.*[19] found that the information provided to patients before implantation of an ICD was sparse hindering the patients in being a part of the decision-making process. This finding could be even more relevant for immigrants who might face social/cultural barriers such as understanding the native language and/or have different perceptions of illness which might lead to misinterpretation of the information regarding their cardiovascular condition and the treatment modalities involved. Moreover, different health behaviours are known to persist between origins for example although we found no association with smoking and all-cause mortality across origins, smoking has previously been found to be related to poor prognosis of heart failure among African–American vs. White patients.[20] Second, of concern, prejudice/discrimination based on race or ethnicity can influence treatment and care of patients with cardiovascular conditions.[21] For example, a study by Breathett *et al.*[21] evaluated how healthcare professionals decision-making process may contribute to racial disparities in advanced treatment of heart failure. When a subgroup of 44 reviewers were asked to discuss individual cases, black patients were more likely to be recommended for ventricular assist device compared with White patients who were more often recommended for heart transplant as they were perceived to display better compliance to follow-up care.[22] Also, many cardiac clinicians might even be unaware of behaviours that could inflict racial/ethnical disparities in cardiac care.[22] Fourth, race and ethnical minorities are often underrepresented in e.g. clinical trials[23] which may be due to limited ability to assess

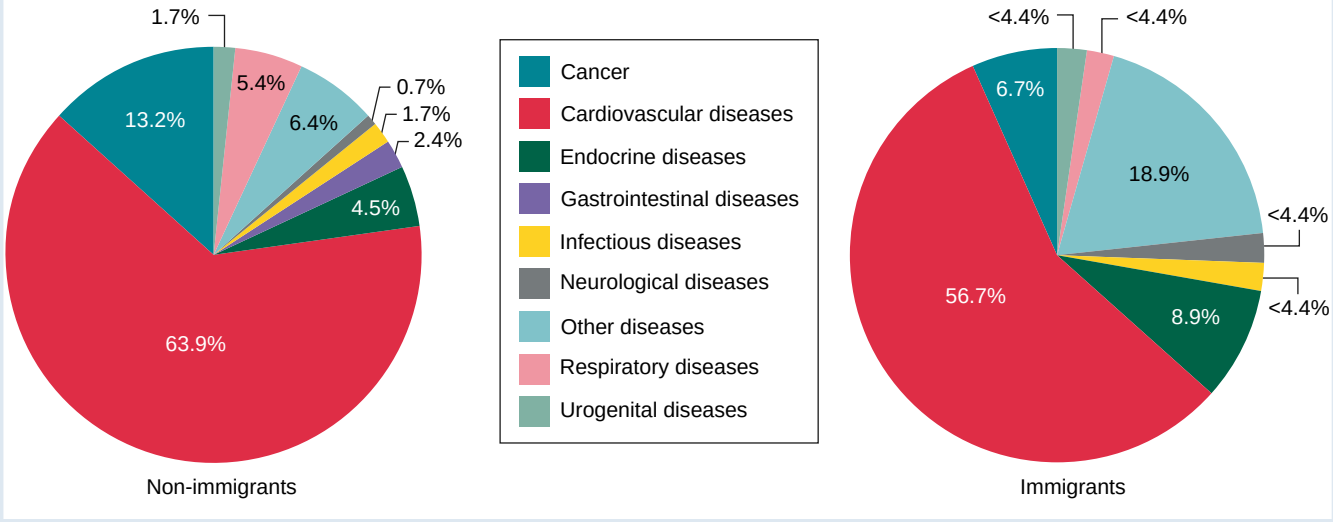


Figure 2 Primary cause of mortality among immigrants and non-immigrants in cardiac resynchronization therapy.

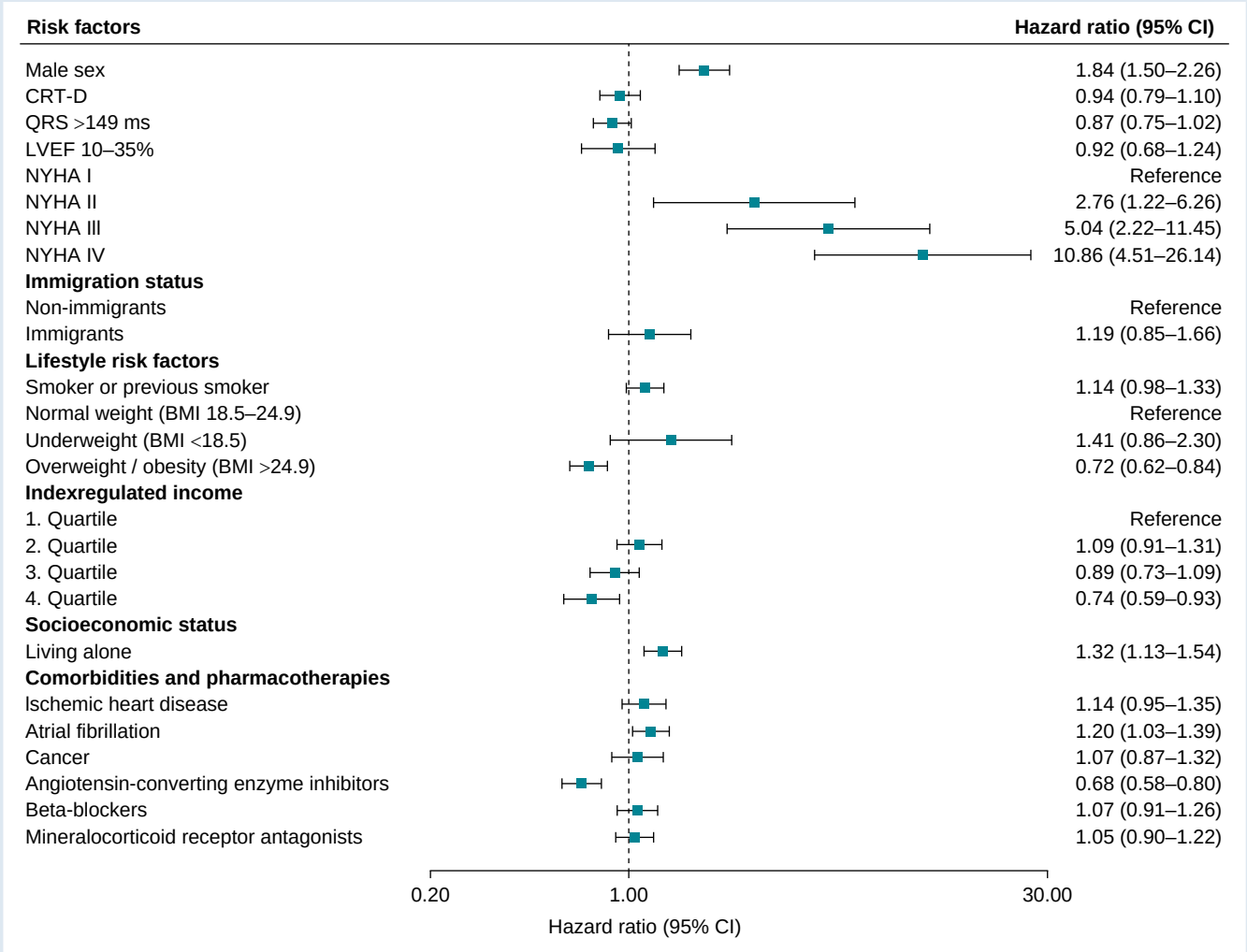


Figure 3 Multivariable Cox regression for all-cause mortality among patients in cardiac resynchronization therapy. Included in the model are listed factors, 5-year increment in age, and year of cardiac resynchronization therapy. BMI, body mass index; CRT-D, cardiac resynchronization therapy-defibrillator; CI, confidence interval; LVEF, left ventricular ejection fraction; ms, millisecond; NYHA, New York Heart Association.

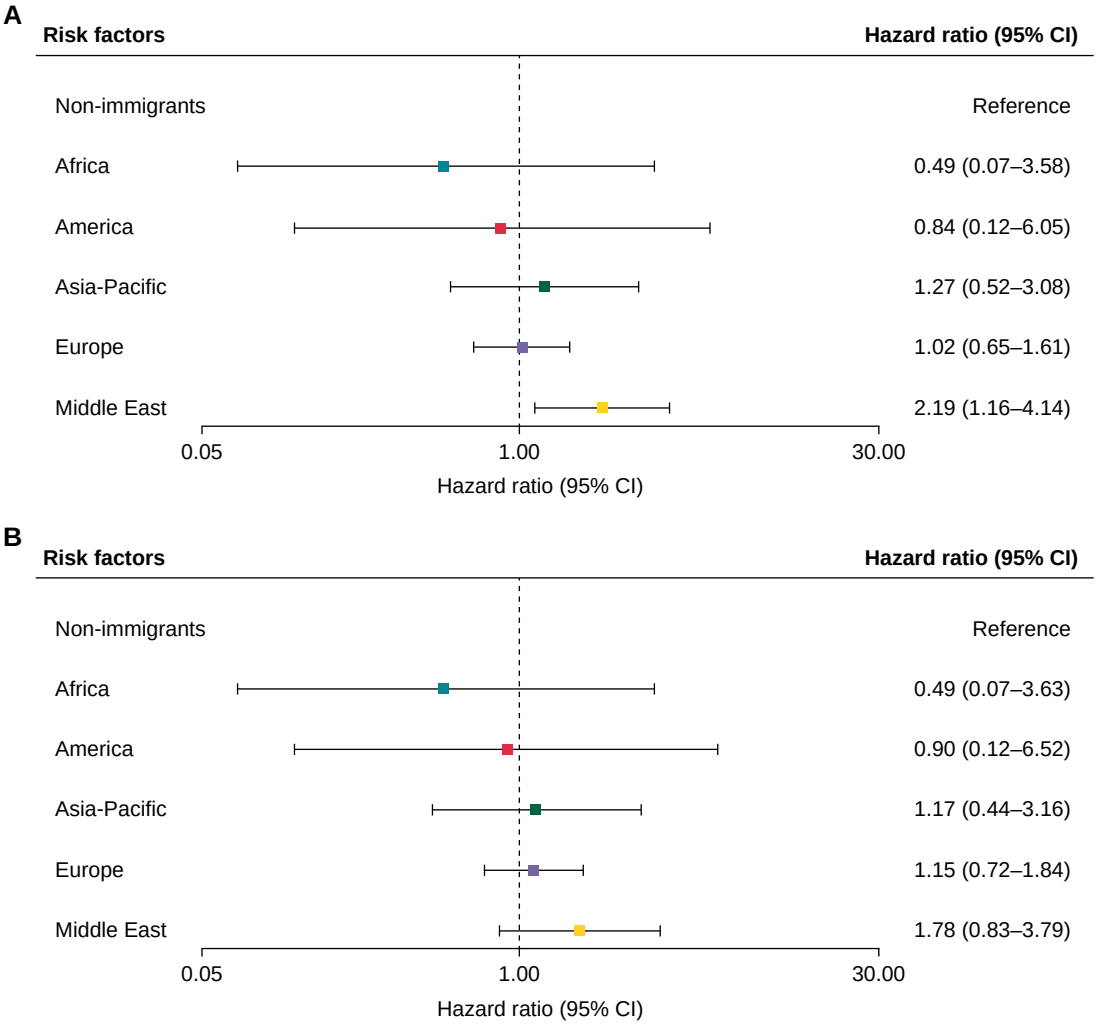


Figure 4 Multivariable Cox regression for all-cause mortality among patients in cardiac resynchronization therapy adjusted for origin. (*A*) Not adjusted for education level, (*B*) adjusted for education level (both models are shown in full length in Supplementary material online, *Figures S2* and *S3*, respectively).

this in an unbiased manner. However, this is diminished in registry-based studies, which consists of an unselected patient cohort.

An American study by Farmer *et al.*,[8] which examined disparities in selection of patients eligible for CRT implantation, found that patients belonging to racial minority groups were less likely to receive a CRT. For example, Blacks and Hispanics were less likely to receive a CRT-D than White patients although both groups met criteria for implantation even though similar survival rates have been reported. Moreover, a study by Ziaeian *et al.*[7] found a significant 24-month reduction in mortality, after CRT/ICD implantation, with no significant interaction by racial/ethnic group. In line with this, no associated difference in 5-year mortality after CRT implantation was found, and also the immigrant population had comparable baseline characteristics as the natives in the present study. However, this finding may be caused by 'the healthy immigrant effect' meaning that people who immigrate have better health than the native population. In comparison, although we did not identify a difference in all-cause mortality between immigrants and non-immigrants, on a general basis, a significant correlation between origin from the Middle East and all-cause mortality after CRT implantation was observed. Heart failure is a multifactorial disease where both environment and genetic play a consequential role.[20] In line with this, we found that immigrants originating from Asia-Pacific and the Middle East were more likely to have obtained basic school as highest completed education compared with patients from Europe and America who had obtained a higher education (i.e. university degree) according to patients in the present. This is consistent with findings from a recent study indicating that lower education levels were associated with increased mortality risk after a heart failure diagnosis.[24]

This finding could partly be explained by lower education level being associated with reduced adherence to pharmacotherapy and therefore to poor outcomes as implicated in a recent study by Oates *et al.*[25] which found that low income and chronic stress were associated with medication non-adherence as well as the odds of non-adherence increased with the accumulation of social risk factors. Of note, in the sensitivity analysis where we adjusted for education level Middle Eastern origin was no longer associated with increased rates of all-cause mortality. The reason not to include education level in the primary adjusted analysis were derived from the marked observed differences seen across different regions and with the rationale to avoid adjustment for the exposure (region of origin), and thereby wrongly attenuating

observed differences. Moreover, several studies have found that income is a better indicator for socioeconomic status than education level.[17,18]

Limitations

The study design lends itself to some limitations which are inherent to all registry-based studies. Therefore, even though we sought to eliminate potential confounders, we acknowledge that our findings could have been influenced by residual confounders as well as the results are associations and not causal relationships and should be treated as such.

We were able to obtain information on immigration status, but the nationwide registries do not contain information on race. The immigrant population was small, and the Danish healthcare system is universal; hence, extrapolation of the results to other healthcare settings and study populations should be done with caution. Also, the subgroups (i.e. origins) of immigrants were small, and a large proportion of the immigrant population originated from Europe which could have influenced our findings. Furthermore, low numbers reduced level of detail for certain regions of origin. The registries can only partly account for potential differences as they do not contain information on e.g. health believes. Furthermore, this study did not have information on the implications for immigration to Denmark, as the registries do not contain this information, and hence were unable to distinguish between patients who moved because of an opportunity (e.g. employment opportunities) and for survival (e.g. to escape a violent conflict). There was a significant age difference between the immigrants and non-immigrants although we sought to adjust for this in the multivariable Cox regression, we cannot exclude the possibility that this could have affected our findings. The Danish registries contain information on diagnoses (including heart failure) but information on heart failure related factors e.g. NYHA functional class and LVEF are not routinely recorded unless the patients receive a device (e.g. CRT). Hence, this information was only available for patients who underwent CRT implantation based on this we were only able to descriptively examine potential differences in the patient selection for CRT between immigrants and non-immigrants.

Conclusion

Among patients undergoing first-time CRT implantation, comparable implantation rates were observed between immigrants and non-immigrants. Additionally, being an immigrant did not show any significant association with risk of hospitalizations related to heart failure or long-term mortality when compared to non-immigrants. However, it should be emphasized that the immigrant population underwent CRT implantation at a significantly younger age than the non-immigrants, warranting attention. Moreover, among immigrants, individuals of Middle Eastern origin had a greater likelihood of all-cause mortality after CRT implantation compared with non-immigrants, whereas this observation was not significant for immigrants of European, African, Asian, or American origin. The findings indicate the benefits of an open healthcare system, as in Denmark, providing equal access to treatment of cardiovascular disease such as heart failure and hence does not result in systematic disadvantages for immigrants.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

Due to restrictions related to Danish law and protecting patient privacy, the combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark. Data will be shared on request to the corresponding author with permission of Statistics Denmark. More information regarding data access is available at https://www.dst.dk/en/TilSalg/Forskningsservice.

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