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DEVICES

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Real-world geographic variations in the use of cardiac implantable electronic devices—The PANORAMA 2 observational cohort study

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Abstract

Background: Currently, several geographies around the world remain underrepresented in medical device trials. The PANORAMA 2 study was designed to assess contemporary region-specific differences in clinical practice patterns of patients with cardiac implantable electronic devices (CIEDs).

Methods: In this prospective, multicenter, observational, multinational study, baseline and implant data of 4,706 patients receiving Medtronic CIEDs (Medtronic plc, Minneapolis, MN, USA; either *de novo* device implants, replacements, or upgrades) were analyzed, consisting of: 54% implantable pulse generators (IPGs), 20.3% implantable cardiac defibrillators (ICDs), 15% cardiac resynchronization therapy -defibrillators, and 5.1% cardiac resynchronization therapy -pacemakers, from 117 hospitals in 23 countries across four geographical regions between 2012 and 2016.

Results: For all device types, in all regions, there were fewer females than males enrolled, and women were less likely to have ischemic cardiomyopathy. Implant procedure duration differed significantly across the geographies for all device types. Subjects from emerging countries, women, and older patients were less likely to receive a magnetic resonance imaging-compatible device. Defibrillation testing differed significantly between the regions. European patients had the highest rates of atrial fibrillation (AF), and the lowest number of implanted single-chamber IPGs. Evaluation of stroke history suggested that the general embolic risk is more strongly associated with stroke than AF.

Conclusions: We provide comprehensive descriptive data on patients receiving Medtronic CIEDs from several geographies, some of which are understudied in randomized controlled trials. We found significant variations in patient characteristics. Several medical decisions appear to be affected by socioeconomic factors. Long-term follow-up data will help evaluate if these variations require adjustments to outcome expectations.

KEYWORDS
cardiac pacing, cardiac resynchronization, defibrillators, global registry, heart failure

1 | INTRODUCTION

Cardiac implantable electronic devices (CIEDs) have become a mainstay of modern cardiovascular medicine. CIEDs include implantable cardioverter-defibrillators (ICDs) and implantable pulse generators (IPGs), i.e., pacemakers—either with or without cardiac resynchronization therapy (CRT)—and insertable cardiac monitors (ICMs). Randomized controlled trials (RCTs) have consistently demonstrated the

effectiveness of device-based therapies and diagnostics for cardiac rhythm and disease management.[1,2] Their use is strongly associated with an improved quality of life and survival, and reduced healthcare utilization.[3,4] As such, clinical trials have proven instrumental in laying out guidelines for the application of these therapies.[5,6]

To inform global clinical practice guidelines clinical trial evidence from a study cohort is often extrapolated to the population of interest in the guideline. However, it is not warranted—without further research—to assume that results from a distinct population in a specific region can be extrapolated to a less well-defined patient population, or to other geographies. It must be acknowledged that regional variations exist in race, genetics,[7] patient demographics, disease incidence,[8,9] comorbidities,[10] and healthcare systems and reimbursement policies.[11,12] Furthermore, differences in cultural attitudes to disease and implant practices should also be considered, as they may affect the choice of therapy, as well as the expected therapeutic outcomes.[13] Moreover, there are discrepancies across distinct geographies in terms of interpretation and treatment of risk factors.[14]

While RCTs are often considered the "gold standard" in evaluating the effectiveness of a therapy in tightly controlled settings, observational studies are designed to assess the relevance and credibility of clinical trial data in real-world settings.[15] Our current insights into the real-world application of cardiac rhythm management (CRM) therapies are predominantly based on data registries conducted in Europe and North America.[16,17] At present, there is a paucity of data pertaining to regional differences in CRM, particularly in relation to demographics, comorbidities, and treatment practices in emerging or developing geographies.

In 2014, the PANORAMA study was published.[18] PANORAMA was a long-term, multicenter, prospective, nonrandomized observational study, designed to collect multinational data on subjects implanted with Medtronic CIEDs (Medtronic plc, Minneapolis, MN, USA). The results of PANORAMA indicated significant variations in age, cardiovascular diseases, rhythm disturbances, type of device implant, and implant practices across the various geographies.[18] The objective of the current study was to expand on the findings of PANORAMA. The goal was to gain more insight into real-world clinical practice by better understanding the practice patterns and economic settings of a larger set of geographies to adequately interpret clinical outcomes.

2 | METHODS

2.1 | Study population

PANORAMA 2 (ClinicalTrials.gov Identifier: NCT01723566) was designed and conducted in compliance with local ethical requirements and according to the principles outlined in the Declaration of Helsinki[19] and the laws and regulations in the countries in which the study was conducted. The study was submitted to locally appointed ethics committees and informed consent was obtained from all subjects. The study included patients that were implanted with a Medtronic market-released CIED (IPGs, ICDs with or without CRT capability, and ICMs; either *de novo* device implants, replacements, or upgrades). ICMs only represented 5.5% of the total study population (n = 4,706), and only a few ICM subjects were recruited outside of Europe (n = 24). ICM data were therefore not considered for any further analyses.

Patients were required to be at least 18 years of age, and were enrolled from the following geographies[20] and countries: Western Europe (Belgium, Denmark, France, Germany, Greece, and Luxemburg), Eastern Europe (Belarus*, Bosnia and Herzegovina*, Lithuania*, Romania*, Russian Federation*, Slovakia*, and Ukraine*), the Middle East (Egypt*, Kuwait*, Saudi Arabia*, and Tunisia*), South Africa*, and Asia (Bangladesh*, China*, India*, Pakistan*, and Taiwan). Out of the 23 participating countries 16 were considered to be emerging or developing economies (indicated with: *) based on the guidelines set out by the International Monetary Fund (IMF).[21] All patients implanted with commercially available Medtronic CIEDs that were used within their intended use and indication could be included in the PANORAMA 2 study.

2.2 | Study design

The PANORAMA 2 clinical study was a prospective, multicenter, multinational, observational study. Patients were assessed at study entry and during follow-up visits for at least 1 year following the implant procedure according to the standard follow-up visit scheme of the participating centers and did not require any procedures beyond regular practice. All treatment decisions were made at the discretion of the treating physician. Initially, the study was designed to enroll 8,500 patients. The PANORAMA 2 database included a total of 4,885 subjects between July 2012 and June 2016. In total, 179 subjects were excluded from the analyzed cohort due to: missing or incorrect informed consent (n = 96), data quality issues (n = 57), violation of the inclusion/exclusion criteria (n = 10), and missing implant dates (n = 16). Treatment duration and follow-up was shorter than originally intended for some subjects due to early study closure.

2.3 | Data collection and measures

Clinical data were collected by the investigators using a study-specific electronic case report form (CRF), and stored in a centralized, secure database. The data collected at baseline included demographics and clinical characteristics, and medical history. The risk factors for cardiovascular disease were smoking, obesity (i.e., body mass index [BMI] $\geq$ 30 kg/m^2), hypertension, hyperlipidemia, diabetes, and age above 65 years. At implant, data were collected on the implant procedure and techniques. The CHA_2DS_2-VASc score was used as a clinical predictor to evaluate the risk of stroke in patients.[22]

2.4 | Statistical analyses

Descriptive statistics were used to summarize patient characteristics. Data are reported with mean and standard deviation for continuous variables and counts and percentages for categorical variables. Each continuous patient characteristic was compared across the regions using an analysis of variance with pairwise

TABLE 1 Overall patient enrollment by region

	Total	Asia	Europe	Middle East	South Africa
Number of patients (% of total)	4706	1519	2491	404	292
		(32.3%)	(52.9%)	(8.6%)	(6.2%)
Number of countries	23	5	13	4	1
Number of sites	117	29	73	8	7
Number, % of patients from emerging countries (% of total patients per region)	1867 (39.7% of total patients)	906 *(59.6%)*	265 *(10.6%)*	404 *(100%)*	292 *(100%)*

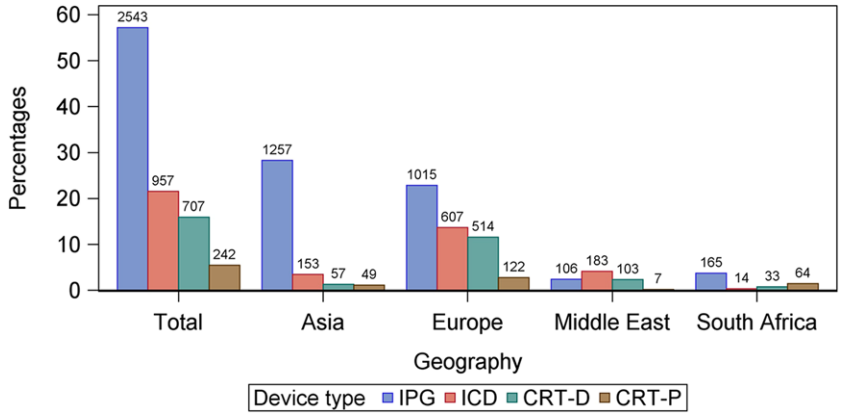

FIGURE 1 Distribution of device types by region. CRT-D = cardiac resynchronization therapy - defibrillator; CRT-P = cardiac resynchronization therapy - pacemaker; ICD = implantable cardiac defibrillator; IPG = pacemaker. [Color figure can be viewed at wileyonlinelibrary.com]

comparisons performed using Bonferroni adjustment. For categorical variables a χ^2 test, Fisher's exact test, or a Cochran-Mantel-Haenszel test was used as appropriate to evaluate differences across regions and for association of two or more categorical patient characteristics. Odds ratios (ORs) were further determined to assess the association between two categorical characteristics. Regression models were employed to examine the effects of different characteristics on implant procedure duration, magnetic resonance imaging (MRI) compatibility of devices, and stroke. SAS software (version 9.4) (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses. P-values less than 0.05 were considered statistically significant. Stratification of the analysis was specified *a priori* by region and device type.

3 | RESULTS

3.1 | Overall baseline demographics and distribution of device characteristics by region

Table 1 provides an overview of the overall patient enrollment by region. Emerging or developing economies accounted for 39.7% (n = 1,867) of the total study population (n = 4,706). The device type distribution by region is shown in Figure 1. Well over half of the study population was implanted with an IPG (54.0%), while ICDs, CRT-defibrillators (CRT-Ds), and CRT-pacemakers (CRT-Ps) accounted for 20.3%, 15.0%, and 5.1%, respectively. All baseline and initial treatment characteristics of subjects implanted with IPG, ICD, CRT-D, and CRT-P devices stratified by region are reported in Tables 2–5, respectively.

3.2 | General epidemiological findings

Overall, European subjects were the oldest, whereas Middle Eastern subjects were the youngest, across almost all device types. In line with published trials, more males than females were included, with percentages of females ranging from 19.4% for CRT-D implants to 43.7% for IPG. Intriguingly, relatively few women were implanted with ICD or CRT-D devices (Table 6). Furthermore, females were less likely to have ischemic cardiomyopathy than males. Overall, cardiovascular risk factors differed between the regions. Diabetes was more prevalent in the Middle East, while hyperlipidemia tended to occur more frequently in South Africa. The highest BMI scores were found in the Middle East, in contrast to Asian patients who had the lowest BMI and demonstrated the lowest number of cardiovascular risk factors for all device types (Tables 2–5). Ischemic cardiomyopathy occurred less frequently in Asia.

3.3 | Implantation and device selection

Implant procedure duration differed significantly across the geographies for all device types (Tables 2–5). In general, procedure duration was shorter in South Africa and Europe compared to Asia and the Middle East for all device types. To ascertain what may have influenced implant procedure duration, several putative predictors were identified (e.g., pulmonary hypertension, tricuspid valve dysfunction, lead introduction site, device replacement, lead revision, device location, obesity, etc.), many of which significantly affected procedure time for each device type on their own. A subsequent multiple regression analysis, including these predictors for each device type, revealed

TABLE 2 Baseline, device, and implant characteristics for the IPG cohort by region

Subject characteristics	Total subjects (N = 2543)	Subjects in Asia (N = 1257)	Subjects in Europe (N = 1015)	Subjects in Middle East (N = 106)	Subjects in South Africa (N = 165)	P-value
Demographics						
Age (years), mean (SD)	71.8 (12.6)	71.2 (12.0)	73.8 (12.4)	63.9 (18.2)	69.4 (11.6)	<0.001
Male	1431 (56.3%)	661 (52.6%)	617 (60.8%)	53 (50.0%)	100 (60.6%)	<0.001
Primary Indication						<0.001
SND	992 (39.0%)	595 (47.3%)	280 (27.6%)	21 (19.8%)	96 (58.2%)	
AV block	1204 (47.3%)	576 (45.8%)	519 (51.1%)	71 (67.0%)	38 (23.0%)	
Syncope	161 (6.3%)	32 (2.5%)	117 (11.5%)	3 (2.8%)	9 (5.5%)	
Ventricular bradycardia	65 (2.6%)	17 (1.4%)	42 (4.1%)	1 (0.9%)	5 (3.0%)	
Other	112 (4.4%)	37 (2.9%)	54 (5.3%)	10 (9.4%)	11 (6.7%)	
Medical history						
Number of risk factors, mean (SD)	2.3 (1.2)	2.1 (1.2)	2.5 (1.3)	2.5 (1.6)	2.5 (1.2)	<0.001
BMI (kg/m^2), mean (SD)	25.9 (4.9)	24.0 (3.8)	27.5 (4.8)	29.6 (5.8)	28.9 (5.7)	<0.001
Overweight/Obese[a]	1313 (51.6%)	456 (36.3%)	666 (65.6%)	86 (81.1%)	105 (63.6%)	<0.001
Past or current smoker	763 (30.0%)	291 (23.2%)	403 (39.7%)	22 (20.8%)	47 (28.5%)	<0.001
Hypertension	1646 (64.7%)	832 (66.2%)	644 (63.4%)	59 (55.7%)	111 (67.3%)	0.126
Hyperlipidemia	934 (36.7%)	309 (24.6%)	479 (47.2%)	58 (54.7%)	88 (53.3%)	<0.001
Diabetes	712 (28.0%)	376 (29.9%)	255 (25.1%)	47 (44.3%)	34 (20.6%)	<0.001
Pulmonary hypertension	156 (6.1%)	71 (5.6%)	66 (6.5%)	14 (13.2%)	5 (3.0%)	0.003
CHA_2DS_2-VASc, mean (SD)	3.3 (1.7)	3.4 (1.7)	3.3 (1.6)	2.7 (1.7)	3.0 (1.5)	<0.001
Stroke	235 (9.2%)	140 (11.1%)	80 (7.9%)	2 (1.9%)	13 (7.9%)	0.002
AF	786 (30.9%)	363 (28.9%)	367 (36.2%)	14 (13.2%)	42 (25.5%)	<0.001
Paroxysmal	452 (17.8%)	200 (15.9%)	220 (21.7%)	4 (3.8%)	28 (17.0%)	<0.001
Persistent/Long-standing persistent/Permanent	311 (12.2%)	155 (12.3%)	135 (13.3%)	7 (6.6%)	14 (8.5%)	0.087
LVEF (%), mean (SD)	60.9 (10.4)	63.1 (10.7)	58.5 (9.2)	56.1 (6.9)	61.7 (12.5)	<0.001
Not reported	1015 (39.9%)	508 (40.4%)	451 (44.4%)	13 (12.3%)	43 (26.1%)	
NYHA Class III + IV	215 (8.5%)	121 (9.6%)	82 (8.1%)	6 (5.7%)	6 (3.6%)	0.048
Implant						
Single-chamber device[b]	432 (17.0%)	280 (22.3%)	93 (9.2%)	30 (28.3%)	29 (17.6%)	<0.001
MRI-compatible[b]	1196 (47.0%)	305 (24.3%)	738 (72.7%)	35 (33.0%)	118 (71.5%)	<0.001
Implantation side						<0.001
Left	2100 (82.6%)	1120 (89.1%)	730 (71.9%)	101 (95.3%)	149 (90.3%)	
Right	439 (17.3%)	136 (10.8%)	282 (27.8%)	5 (4.7%)	16 (9.7%)	
Procedure duration (min), mean (SD)	61.3 (31.0)	70.9 (31.5)	50.4 (23.0)	79.8 (32.9)	37.3 (30.4)	<0.001

Note: For variables with multiple categories, percentages may not sum up to 100% due to missing data or other response options. P-values are based on comparison of presented categories.

[a]Overweight defined as BMI (kg/m^2) between 25 and 29 and obese defined as BMI ≥ 30.

[b]Countries with relevant device enrollment restrictions were excluded from calculation of a P-value.

AF = atrial fibrillation; AV = atrioventricular; BMI = body mass index; IPG = implantable pulse generator; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; SD = standard deviation; SND = sinus node dysfunction.

that the geographical region remained relevant as a factor influencing implant procedure duration for each device type (data not shown).

Most pacemakers (IPGs) were dual-chamber devices (83% vs 17% single-chamber). The rate of implanted single-chamber IPGs was significantly higher in the Middle East, Asia, and South Africa compared to Europe (Figure 2, Table 2). Furthermore, 58% of all ICDs were single-chamber, and 42% were dual-chamber devices, respectively (Figure 2).

Subclavian vein cannulation was by far the most frequent venous access method for all device types and geographies, but cephalic vein cut-down was more often used in Europe (data not shown). ICD defibrillation testing is still performed in a relevant number of ICD/CRT-D recipients. However, there are significant differences between the regions (Tables 3 and 4). There was a relevant number of patients with a QRS duration < 120 ms or a nonleft bundle branch block morphology

TABLE 3 Baseline, device, and implant characteristics for the ICD cohort by region

Subject characteristics	Total subjects (N = 957)	Subjects in Asia (N = 153)	Subjects in Europe (N = 607)	Subjects in Middle East (N = 183)	Subjects in South Africa (N = 14)	P-value
Demographics						
Age (years), mean (SD)	61.0 (14.4)	60.6 (14.4)	61.8 (14.4)	58.2 (14.1)	68.1 (9.9)	0.006
Male	768 (80.3%)	117 (76.5%)	482 (79.4%)	159 (86.9%)	10 (71.4%)	0.060
Primary indication						<0.001
Secondary prevention	426 (44.5%)	76 (49.7%)	286 (47.1%)	55 (30.1%)	9 (64.3%)	
Primary prevention	531 (55.5%)	77 (50.3%)	321 (52.9%)	128 (69.9%)	5 (35.7%)	
Medical history						
Number of risk factors, mean (SD)	2.2 (1.4)	1.5 (1.2)	2.2 (1.4)	2.6 (1.5)	2.9 (1.1)	<0.001
BMI (kg/m^2), mean (SD)	27.2 (5.1)	24.8 (3.2)	27.2 (5.1)	28.8 (5.7)	29.6 (5.1)	<0.001
Overweight/Obese[a]	591 (61.8%)	67 (43.8%)	383 (63.1%)	132 (72.1%)	9 (64.3%)	<0.001
Past or current smoker	463 (48.4%)	50 (32.7%)	336 (55.4%)	71 (38.8%)	6 (42.9%)	<0.001
Hypertension	481 (50.3%)	67 (43.8%)	301 (49.6%)	104 (56.8%)	9 (64.3%)	0.089
Hyperlipidemia	496 (51.8%)	35 (22.9%)	342 (56.3%)	109 (59.6%)	10 (71.4%)	<0.001
Diabetes	271 (28.3%)	35 (22.9%)	138 (22.7%)	94 (51.4%)	4 (28.6%)	<0.001
Pulmonary hypertension	113 (11.8%)	16 (10.5%)	57 (9.4%)	40 (21.9%)	0 (0.0%)	<0.001
CHA_2DS_2-VASc, mean (SD)	2.7 (1.6)	2.6 (1.5)	2.6 (1.7)	3.0 (1.7)	3.3 (1.4)	0.016
Stroke	59 (6.2%)	6 (3.9%)	40 (6.6%)	12 (6.6%)	1 (7.1%)	0.674
Myocardial infarction	430 (44.9%)	61 (39.9%)	274 (45.1%)	89 (48.6%)	6 (42.9%)	0.380
AF	251 (26.2%)	38 (24.8%)	183 (30.1%)	27 (14.8%)	3 (21.4%)	<0.001
Paroxysmal	126 (13.2%)	20 (13.1%)	94 (15.5%)	11 (6.0%)	1 (7.1%)	0.008
Persistent/Long-standing persistent/Permanent	114 (11.9%)	14 (9.2%)	83 (13.7%)	15 (8.2%)	2 (14.3%)	0.142
LVEF (%), mean (SD)	37.2 (14.1)	42.9 (16.7)	38.0 (13.2)	30.5 (10.6)	45.8 (20.6)	<0.001
Not reported	258 (27.0%)	25 (16.3%)	208 (34.3%)	17 (9.3%)	8 (57.1%)	
NYHA Class						<0.001
No HF	255 (26.6%)	50 (32.7%)	169 (27.8%)	30 (16.4%)	6 (42.9%)	
I	110 (11.5%)	10 (6.5%)	87 (14.3%)	12 (6.6%)	1 (7.1%)	
II	299 (31.2%)	39 (25.5%)	179 (29.5%)	77 (42.1%)	4 (28.6%)	
III	181 (18.9%)	37 (24.2%)	91 (15.0%)	50 (27.3%)	3 (21.4%)	
IV	34 (3.6%)	10 (6.5%)	12 (2.0%)	12 (6.6%)	0 (0.0%)	
Cardiomyopathy	708 (74.0%)	67 (43.8%)	481 (79.2%)	155 (84.7%)	5 (35.7%)	<0.001
Ischemic	474 (49.5%)	43 (28.1%)	313 (51.6%)	113 (61.7%)	5 (35.7%)	
Nonischemic	234 (24.5%)	24 (15.7%)	168 (27.7%)	42 (23.0%)	0 (0.0%)	
QRS duration ≥ 120 ms	278 (29.0%)	50 (32.7%)	175 (28.8%)	47 (25.7%)	6 (42.9%)	0.097
Not reported	112 (11.7%)	8 (5.2%)	96 (15.8%)	5 (2.7%)	3 (21.4%)	
Implant						
Single-chamber device[b]	555 (58.0%)	99 (64.7%)	325 (53.5%)	124 (67.8%)	7 (50.0%)	0.004
MRI-compatible[b]	159 (16.6%)	2 (1.3%)	126 (20.8%)	26 (14.2%)	5 (35.7%)	<0.001
Implantation side						0.056
Left	917 (95.8%)	150 (98.0%)	573 (94.4%)	180 (98.4%)	14 (100.0%)	
Right	38 (4.0%)	3 (2.0%)	32 (5.3%)	3 (1.6%)	0 (0.0%)	
Procedure duration (min), mean (SD)	63.6 (37.1)	90.0 (47.4)	50.5 (26.8)	80.9 (35.0)	54.4 (36.2)	<0.001
Defibrillation testing performed	133 (13.9%)	38 (24.8%)	92 (15.2%)	0 (0.0%)	3 (21.4%)	<0.001

Note: For variables with multiple categories, percentages may not sum up to 100% due to missing data or other response options. P-values are based on comparison of presented categories.

[a]Overweight defined as BMI (kg/m^2) between 25 and 29 and obese defined as BMI ≥ 30.

[b]Countries with relevant device enrollment restrictions were excluded from calculation of a P-value.

AF = atrial fibrillation; BMI = body mass index; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NYHA = New York Heart Association; SD = standard deviation.

TABLE 4 Baseline, device, and implant characteristics for the CRT-D cohort by region

Subject characteristics	Total subjects (N = 707)	Subjects in Asia (N = 57)	Subjects in Europe (N = 514)	Subjects in Middle East (N = 103)	Subjects in South Africa (N = 33)	P-value
Demographics						
Age (years), mean (SD)	66.3 (11.2)	62.4 (11.0)	68.0 (10.1)	59.4 (13.0)	67.6 (11.5)	<0.001
Male	570 (80.6%)	43 (75.4%)	417 (81.1%)	83 (80.6%)	27 (81.8%)	0.778
Medical history						
Number of risk factors, mean (SD)	2.5 (1.3)	1.6 (1.2)	2.6 (1.3)	2.9 (1.3)	2.6 (1.2)	<0.001
Not reported	33 (4.7%)	0 (0.0%)	25 (4.9%)	0 (0.0%)	8 (24.2%)	
BMI (kg/m^2), mean (SD)	28.0 (5.3)	24.0 (3.6)	28.1 (5.0)	29.7 (6.2)	28.7 (6.5)	<0.001
Not reported	23 (3.3%)	0 (0.0%)	15 (2.9%)	0 (0.0%)	8 (24.2%)	
Overweight/Obese[a]	468 (66.2%)	22 (38.6%)	351 (68.3%)	78 (75.7%)	17 (51.5%)	<0.001
Past or current smoker	344 (48.7%)	22 (38.6%)	266 (51.8%)	38 (36.9%)	18 (54.5%)	0.008
Hypertension	415 (58.7%)	28 (49.1%)	302 (58.8%)	67 (65.0%)	18 (54.5%)	0.314
Hyperlipidemia	398 (56.3%)	16 (28.1%)	293 (57.0%)	64 (62.1%)	25 (75.8%)	<0.001
Diabetes	250 (35.4%)	18 (31.6%)	161 (31.3%)	67 (65.0%)	4 (12.1%)	<0.001
Myocardial infarction	204 (28.9%)	16 (28.1%)	151 (29.4%)	23 (22.3%)	14 (42.4%)	0.113
Pulmonary hypertension	105 (14.9%)	9 (15.8%)	60 (11.7%)	33 (32.0%)	3 (9.1%)	<0.001
CHA_2DS_2-VASc, mean (SD)	3.3 (1.6)	3.0 (1.6)	3.3 (1.7)	3.1 (1.6)	3.1 (1.1)	0.313
Stroke	52 (7.4%)	3 (5.3%)	46 (8.9%)	2 (1.9%)	1 (3.0%)	0.045
AF	264 (37.3%)	11 (19.3%)	223 (43.4%)	14 (13.6%)	16 (48.5%)	<0.001
Paroxysmal	100 (14.1%)	7 (12.3%)	82 (16.0%)	4 (3.9%)	7 (21.2%)	0.010
Persistent/Long-standing persistent/Permanent	154 (21.8%)	3 (5.3%)	136 (26.5%)	6 (5.8%)	9 (27.3%)	<0.001
Cardiomyopathy	659 (93.2%)	44 (77.2%)	482 (93.8%)	103 (100.0%)	30 (90.9%)	<0.001
Ischemic	315 (44.6%)	19 (33.3%)	233 (45.3%)	46 (44.7%)	17 (51.5%)	
Nonischemic	343 (48.5%)	25 (43.9%)	248 (48.2%)	57 (55.3%)	13 (39.4%)	
LVEF (%), mean (SD)	30.2 (10.7)	29.1 (10.4)	31.2 (10.6)	25.2 (9.0)	33.8 (13.1)	<0.001
Not reported	175 (24.8%)	5 (8.8%)	142 (27.6%)	19 (18.4%)	9 (27.3%)	
NYHA Class						<0.001
No HF	20 (2.8%)	1 (1.8%)	16 (3.1%)	1 (1.0%)	2 (6.1%)	
I	51 (7.2%)	1 (1.8%)	44 (8.6%)	2 (1.9%)	4 (12.1%)	
II	232 (32.8%)	13 (22.8%)	167 (32.5%)	40 (38.8%)	12 (36.4%)	
III	311 (44.0%)	28 (49.1%)	226 (44.0%)	47 (45.6%)	10 (30.3%)	
IV	41 (5.8%)	14 (24.6%)	10 (1.9%)	13 (12.6%)	4 (12.1%)	
QRS duration (ms)						
Not reported	151 (21.4%)	5 (8.8%)	124 (24.1%)	14 (13.6%)	8 (24.2%)	
<120	62 (8.8%)	9 (15.8%)	35 (6.8%)	9 (8.7%)	9 (27.3%)	
120 to 150	187 (26.4%)	19 (33.3%)	130 (25.3%)	30 (29.1%)	8 (24.2%)	
>150	307 (43.4%)	24 (42.1%)	225 (43.8%)	50 (48.5%)	8 (24.2%)	
LBBB	487 (68.9%)	34 (59.6%)	357 (69.5%)	80 (77.7%)	16 (48.5%)	0.007
Implant						
Implantation side						<0.001
Left	659 (93.2%)	57 (100.0%)	467 (90.9%)	102 (99.0%)	33 (100.0%)	
Right	45 (6.4%)	0 (0.0%)	44 (8.6%)	1 (1.0%)	0 (0.0%)	
LV lead location						<0.001
Apical	195 (27.6%)	12 (21.1%)	113 (22.0%)	50 (48.5%)	20 (60.6%)	
Nonapical	442 (62.5%)	39 (68.4%)	342 (66.5%)	49 (47.6%)	12 (36.4%)	

(Continues)

TABLE 4 (Continued)

Subject characteristics	Total subjects (N = 707)	Subjects in Asia (N = 57)	Subjects in Europe (N = 514)	Subjects in Middle East (N = 103)	Subjects in South Africa (N = 33)	P-value
Procedure duration (min), mean (SD)	95.2 (66.0)	150.8 (88.9)	80.8 (54.9)	137.0 (69.3)	65.0 (29.9)	<0.001
Defibrillation testing performed	72 (10.2%)	2 (3.5%)	62 (12.1%)	0 (0.0%)	8 (24.2%)	<0.001

Note: For variables with multiple categories, percentages may not sum up to 100% due to missing data or other response categories. P-values are based on comparison of presented categories.

[a]Overweight defined as BMI (kg/m^2) between 25 and 29 and obese defined as BMI ≥ 30.

AF = atrial fibrillation; BMI = body mass index; CRT-D = cardiac resynchronization therapy - defibrillator; HF = heart failure; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

implanted with a CRT device. An apical position of the coronary sinus lead in CRT-D and CRT-P devices ranged between 14.3% (CRT-P, Asia) and 68.8% (CRT-P, South Africa) (Tables 4 and 5).

3.4 | MRI-compatible devices

For the IPG cohort, a logistic multiple regression model was employed to assess the effect of age, gender, and origin of the patient (emerging vs nonemerging country) on whether MRI-compatible devices were used. In a second step, the effect of primary indication (sinus node dysfunction [SND]: yes/no, atrioventricular [AV] block: yes/no, syncope: yes/no) was assessed. Syncope showed a significant effect (P < 0.001), whereas AV block (P = 0.802) and SND (P = 0.320) showed no significant effect for the use of MRI-conditional device. As such, we restricted the results to the model with age, gender, origin, and syncope indication.

The total number of implanted MRI-compatible IPGs was 1,196 (47.0% of all IPG devices). Female patients were at lower odds of receiving an MRI-compatible device (OR = 0.681, 95% confidence interval [CI]: 0.569–0.817, P < 0.001). Strikingly, if patients were 1 year older, their chance of receiving an MRI-compatible IPG was lower (OR = 0.985, 95% CI: 0.977–0.992, P < 0.001). In emerging countries, the odds of receiving an MRI-conditional device were only 0.138 (95% CI: 0.113–0.169, P < 0.001) compared to nonemerging countries. Syncope patients were at higher odds of being implanted with an MRI-compatible device than subjects without syncope (OR = 2.485, 95% CI: 1.692–3.649, P < 0.001).

The total number of implanted MRI-compatible ICDs was 159 (16.6%). For ICD patients, a logistic multiple regression was used to assess the effect of age, gender, origin, and ICD indication (primary vs secondary). Similar to the IPG cohort, an increase in the patient's age with 1 year lowered the chance of receiving an MRI-compatible device (OR = 0.983, 95% CI: 0.972–0.995, P = 0.007). Gender was not significantly different for ICD patients with or without an MRI-conditional device (P = 0.454). As observed in the IPG cohort, patients from emerging countries were less likely to be implanted with an MRI-compatible device than patients from nonemerging countries (OR = 0.321, 95% CI: 0.210–0.489, P < 0.001). Patients with secondary prevention for sudden cardiac death (SCD) were at lower odds of receiving an MRI-compatible device than subjects with primary prevention (OR = 0.417, 95% CI: 0.285–0.609, P < 0.001) (Figure 3).

3.5 | Occurrence of stroke and atrial fibrillation (AF)

European patients had the highest rates of AF for IPG (36.2%), ICD (30.1%), and CRT-P (41.8%), while for CRT-D South African subjects had the highest percentage of AF (48.5% in South Africa and 43.4% in Europe). The incidence of AF was the lowest in the Middle East (Tables 2–5). Patients with AF were at very high odds of receiving oral anticoagulation (OR = 61.6392, 95% CI: 48.9030–77.6924, P < 0.001) compared to patients with no AF. At baseline, the OR for a patient with AF to have had a stroke was 2.0 versus subjects with no AF (OR = 2.0114, 95% CI: 1.6252–2.4894, P < 0.001). This result was similar across the regions. Our data also affirmed the association between hyperlipidemia and stroke (OR = 1.5881, 95% CI: 1.2860–1.9612, P < 0.001). The CHA_2DS_2-VASc scores differed significantly across the regions. The mean CHA_2DS_2-VASc score was lowest in the Middle East with 2.96 compared with the highest in Asia (3.26). A logistic regression model was used to determine which baseline factors were associated with stroke at baseline. Region, AF, and CHA_2DS_2-VASc score were all identified as significant correlates. A one-point increase in the CHA_2DS_2-VASc score (OR = 2.828, 95% CI: 2.570–3.111, P < 0.001) had a stronger relationship with stroke at baseline, i.e., higher OR, than AF (OR = 1.452, 95% CI: 1.135–1.856, P = 0.003).

4 | DISCUSSION

Our current insights into the real-world application of CRM therapies are predominantly based on studies conducted in Europe and North America.[16,17] However, worldwide only roughly 20% of the total number of pacemakers and 40% of all defibrillators are implanted in the United States.[23] Despite the challenges associated with conducting research outside of the usual Western settings, the significance of including CRM data from other geographies should not be underrated. The PANORAMA 2 registry provides additional, worldwide, observational CRM data collected from patients receiving Medtronic CIEDs.

4.1 | General epidemiological findings

European subjects tended to be older than Middle Eastern and Asian subjects, which was in line with a recent World Health Organization report on health and ageing.[24] BMI differed significantly between geographies for all device types. In general, Asian subjects had a lower BMI than their European, Middle Eastern, or South African

TABLE 5 Baseline, device, and implant characteristics for the CRT-P cohort by region

Subject characteristics	Total subjects (N = 242)	Subjects in Asia (N = 49)	Subjects in Europe (N = 122)	Subjects in Middle East (N = 7)	Subjects in South Africa (N = 64)	P-value
Demographics						
Age (years), mean (SD)	67.5 (12.5)	62.1 (12.9)	71.6 (11.3)	68.9 (14.0)	63.5 (11.6)	<0.001
Male	150 (62.0%)	29 (59.2%)	76 (62.3%)	6 (85.7%)	39 (60.9%)	0.653
Medical history						
Number of risk factors, mean (SD)	2.2 (1.3)	1.9 (1.3)	2.4 (1.3)	2.6 (2.1)	2.2 (1.2)	0.102
BMI (kg/m^2), mean (SD)	27.1 (5.8)	24.4 (4.0)	27.3 (4.9)	29.2 (3.2)	28.6 (7.7)	<0.001
Overweight/Obese[a]	146 (60.3%)	18 (36.7%)	79 (64.8%)	7 (100.0%)	42 (65.6%)	<0.001
Past or current smoker	94 (38.8%)	17 (34.7%)	42 (34.4%)	6 (85.7%)	29 (45.3%)	0.042
Hypertension	139 (57.4%)	25 (51.0%)	69 (56.6%)	5 (71.4%)	40 (62.5%)	0.652
Hyperlipidemia	103 (42.6%)	11 (22.4%)	55 (45.1%)	3 (42.9%)	34 (53.1%)	0.013
Diabetes	80 (33.1%)	23 (46.9%)	40 (32.8%)	2 (28.6%)	15 (23.4%)	0.054
Pulmonary hypertension	46 (19.0%)	8 (16.3%)	26 (21.3%)	1 (14.3%)	11 (17.2%)	0.800
CHA_2DS_2-VASc, mean (SD)	3.4 (1.4)	3.2 (1.6)	3.6 (1.4)	3.1 (1.2)	3.1 (1.4)	0.066
Stroke	14 (5.8%)	1 (2.0%)	4 (3.3%)	0 (0.0%)	9 (14.1%)	0.028
AF	83 (34.3%)	10 (20.4%)	51 (41.8%)	2 (28.6%)	20 (31.3%)	0.047
Paroxysmal	25 (10.3%)	6 (12.2%)	14 (11.5%)	0 (0.0%)	5 (7.8%)	0.645
Persistent/Long-standing persistent/Permanent	54 (22.3%)	3 (6.1%)	35 (28.7%)	1 (14.3%)	15 (23.4%)	0.007
Cardiomyopathy	188 (77.7%)	30 (61.2%)	108 (88.5%)	7 (100.0%)	43 (67.2%)	<0.001
Ischemic	83 (34.3%)	10 (20.4%)	45 (36.9%)	5 (71.4%)	23 (35.9%)	
Non-ischemic	105 (43.4%)	20 (40.8%)	63 (51.6%)	2 (28.6%)	20 (31.3%)	
LVEF (%), mean (SD)	34.2 (14.2)	30.6 (10.8)	32.5 (10.2)	30.5 (11.4)	40.2 (20.1)	0.003
Not reported	57 (23.6%)	15 (30.6%)	28 (23.0%)	1 (14.3%)	13 (20.3%)	
NYHA Class						<0.001
No HF	16 (6.6%)	0 (0.0%)	4 (3.3%)	0 (0.0%)	12 (18.8%)	
I	10 (4.1%)	3 (6.1%)	1 (0.8%)	0 (0.0%)	6 (9.4%)	
II	44 (18.2%)	6 (12.2%)	19 (15.6%)	2 (28.6%)	17 (26.6%)	
III	131 (54.1%)	27 (55.1%)	82 (67.2%)	3 (42.9%)	19 (29.7%)	
IV	30 (12.4%)	13 (26.5%)	6 (4.9%)	2 (28.6%)	9 (14.1%)	
QRS duration (ms)						
Not reported	38 (15.7%)	3 (6.1%)	22 (18.0%)	0 (0.0%)	13 (20.3%)	
<120	44 (18.2%)	6 (12.2%)	8 (6.6%)	1 (14.3%)	29 (45.3%)	
120 to 150	58 (24.0%)	12 (24.5%)	33 (27.0%)	3 (42.9%)	10 (15.6%)	
>150	102 (42.1%)	28 (57.1%)	59 (48.4%)	3 (42.9%)	12 (18.8%)	
LBBB	129 (53.3%)	32 (65.3%)	75 (61.5%)	4 (57.1%)	18 (28.1%)	<0.001
Implant						
Implantation side						0.011
Left	215 (88.8%)	48 (98.0%)	101 (82.8%)	6 (85.7%)	60 (93.8%)	
Right	26 (10.7%)	1 (2.0%)	21 (17.2%)	0 (0.0%)	4 (6.3%)	
LV lead location						<0.001
Apical	90 (37.2%)	7 (14.3%)	36 (29.5%)	3 (42.9%)	44 (68.8%)	
Nonapical	133 (55.0%)	37 (75.5%)	79 (64.8%)	4 (57.1%)	13 (20.3%)	
Procedure duration (min), mean (SD)	94.9 (65.9)	142.8 (74.1)	86.3 (44.6)	181.4 (50.9)	61.0 (57.1)	<0.001
Not reported	32 (13.2%)	0 (0.0%)	32 (26.2%)	0 (0.0%)	0 (0.0%)	

Note: For variables with multiple categories, percentages may not sum up to 100% due to missing data or other response categories. P-values are based on comparison of presented categories.

[a]Overweight defined as BMI (kg/m^2) between 25 and 29 and obese defined as BMI ≥ 30.

AF = atrial fibrillation; BMI = body mass index; CRT-P = cardiac resynchronization therapy - pacemaker; HF = heart failure; LBBB = left bundle branch block; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

TABLE 6 Distribution of device types by gender and age

	Total (n = 4706)	IPG (n = 2543)	ICD (n = 957)	CRT-D (n = 707)	CRT-P (n = 242)
Male (n, %)	3062 (65.1%)	1431 (56.3%)	768 (80.3%)	570 (80.6%)	150 (62.0%)
Female (n, %)	1644 (34.9%)	1112 (43.7%)	189 (19.7%)	137 (19.4%)	92 (38.0%)
Mean age (SD)	67.9 (13.9)	71.8 (12.6)	61.0 (14.4)	66.3 (11.2)	67.5 (12.5)

CRT-D = cardiac resynchronization therapy - defibrillator; CRT-P = cardiac resynchronization therapy - pacemaker; ICD = implantable cardiac defibrillator; IPG = pacemaker; SD = standard deviation.

counterparts, which was in agreement with the PANORAMA study.[18] Moreover, Asian CIED recipients demonstrated the lowest number of risk factors for cardiovascular disease for all device types, which may partially be explained by the lower BMI and lower percentage of hyperlipidemia in Asia. Moreover, also in accordance with PANORAMA,[18] patients in the Middle East were distinct from those in other regional groups in terms of the high prevalence of Type II diabetes for all device types, except CRT-P. High incidence of diabetes in the Middle East has been previously described, and likely reflects genetic and environmental differences and dietary preferences.[10,25,26] The inclusion of fewer females in cardiac device trials is a common observation and its explanation is multifactorial. Cardiovascular disease awareness (i.e., diagnosis) in women remains largely inadequate in both patients as well as among physicians.[27] Moreover, traditionally the risk-benefit ratio for device-based therapy has been perceived to be less favorable in women, which may also explain the lesser proportion of enrolled female patients. Another contributing factor may be the fact that fewer women than men meet indications for device therapy (e.g., ICD), as women with heart failure are more likely to have preserved ejection fraction, making them ineligible for defibrillator implantation.[28]

4.2 | Implantation and device selection

Recent reports from the European Heart Rhythm Association (EHRA) demonstrated that a significant heterogeneity exists within the European Society of Cardiology (ESC) member countries with regards to healthcare organization, CIED reimbursement policies, copayment for invasive procedures, availability of a national certification program, required certification for implanting physicians, quality control, lack of manpower, and possible restrictions to treatment availability.[12,29] In addition to distinctive cultural and ethnic characteristics, all these factors may potentially contribute to considerable regional variations in the use of available CIED technology. Unfortunately, structured data comparable to the EHRA White Book are lacking for the Middle East, Asia, and South Africa. Therefore, a short survey was sent to the PANORAMA2 investigators and the data are presented in Supplementary Table S1. In various non-ESC member countries such as South Africa and Saudi Arabia, most people (75–80%) must rely on state-funded healthcare, which often lacks resources for implantation procedures. In countries with lack of state funding for device implantation, patient selection for implantation is likely biased by socioeconomic status as significant out of pocket payments are often required.

Implant procedure duration differed significantly across the geographies for all devices. Additional analysis revealed that none of the variables that may have influenced procedure duration was sufficient to explain the observed regional differences. This apparent discrepancy in implant procedure duration across the regions may likely reflect differences in the experience of the implanting physician, the type of hospital (e.g., academic vs peripheral hospital), and the number of hospital staff present during the implant; all of which are factors not likely to be registered during these procedures.

At present, it is the responsibility of the implanting physician to decide whether to implant a (more expensive) MRI-conditional device. Currently, there is no consensus regarding who should receive an MRI-conditional pacemaker or ICD. Opinions range from universal adoption to almost complete dismissal.[30] Our results demonstrated that older patients and subjects from emerging countries were less likely to be implanted with an MRI-compatible device. There is no apparent medical explanation for our findings that females were at lower odds to be implanted with a MRI-conditional IPG, and that patients with secondary indication for prevention of SCD were less likely to receive MRI-conditional ICDs. It is estimated that up to 75% of all CIED patients are expected to develop an indication for an MRI scan over the lifetime of their device.[31] Therefore, as long as not all IPGs are MRI-conditional, and MRI-compatible devices remain more expensive, the real challenge is to identify the patients not requiring MR imaging in the future. Because this is almost impossible in most patients at the time of CIED implantation, it should be a fundamental requirement that the available MRI technology replaces conventional devices as state-of-the-art treatment.

Our data demonstrated that in certain geographies (e.g., South Africa and the Middle East), the apical position of uni- or bipolar coronary sinus leads is still preferred, in spite of evidence suggesting that left ventricular pacing in the apical region is associated with an unfavorable outcome in CRT recipients.[32,33] This issue has been solved by introducing 4-polar leads that allow basal pacing even in an apical wedge position.

4.3 | Occurrence of stroke and AF

The diagnosis of AF appeared to be low in the Middle East and high in Europe. For all device types, emerging countries demonstrated a lower percentage of AF diagnosis than nonemerging countries. It is unclear, however, whether these differences in AF are due to a true difference in AF incidence or a difference in the diagnosis of AF. It is striking that—despite a lower rate of persistent or permanent AF in the Middle East, South Africa, and Asia—the rate of implanted single-chamber IPGs was significantly higher in these regions compared to Europe. Regarding a history of stroke, no clear geographical pattern

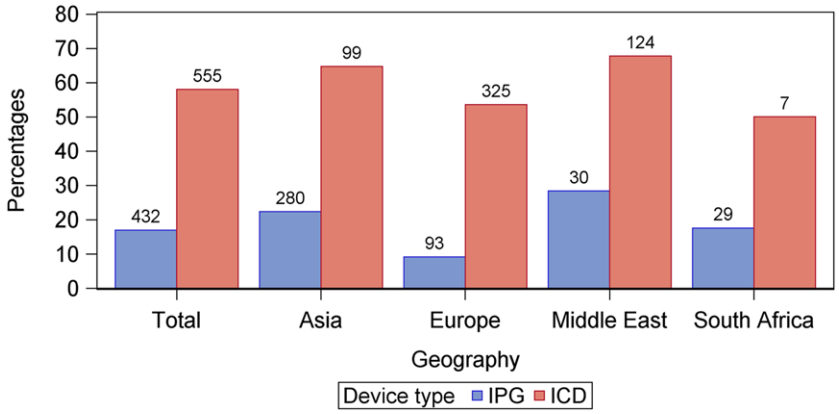

FIGURE 2 Percentage of single-chamber IPG and ICD devices by region. ICD = implantable cardiac defibrillator; IPG = pacemaker; [Color figure can be viewed at wileyonlinelibrary.com]

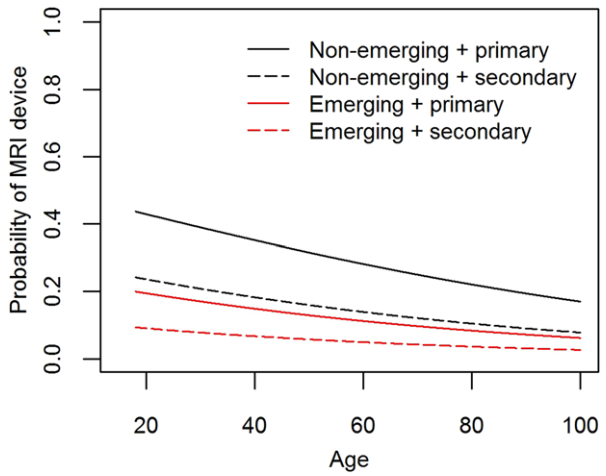

FIGURE 3 Probability of receiving a MRI-compatible ICD depending on age, origin, and indication (primary vs secondary prevention of sudden cardiac death). ICD = implantable cardiac defibrillator; MRI = magnetic resonance imaging [Color figure can be viewed at wileyonlinelibrary.com]

could be discerned. Our baseline results corroborated the previously established relationship between AF and stroke and affirmed the association between hyperlipidemia and stroke. The current discussion is centered around whether AF really causes stroke or whether AF is merely a sign of a general risk profile. Some evidence suggests that small amounts of AF, regardless of symptoms, may be correlated with increased stroke risk.[34] Interestingly, our data suggested that a one-point increase in the CHA_2DS_2-VASc score had a stronger association with stroke than AF. This may point to either underdiagnosed AF, or this finding is in support of the hypothesis that the general embolic risk may be a more important cause for stroke than AF. This might suggest that AF is only a sign of general risk and stroke is caused by a combination of the factors building the general risk profile, a notion which is line with a recent report advocating the need for a paradigm shift in the contribution of AF to stroke.[35] Nevertheless, it should be noted that the strong association between the CHA_2DS_2-VASc score and stroke may also be—at least in part—due to the fact that stroke is an integral part of this score.

4.4 | Limitations

As PANORAMA 2 concerns a single-manufacturer sponsored study, certain specific device characteristics may limit the applicability of the data across all device manufacturers. However, we sought to compare general therapy parameters that would apply regardless of the manufacturer. Even though PANORAMA 2 was a multinational study, some regions of the world were not represented. Furthermore, even within the regions under study, there are substantial differences between single countries and ethnic groups as presented in Supplementary Table S1, but also regarding risk scores, diets, etc. Therefore, following this global comparison, more detailed analysis of specific local data within every single region is scheduled.

Moreover, the number of participating countries and centers may not have been sufficient to accurately characterize the full regional practice, and some of the observed differences could have been center-specific, e.g., some countries limited the enrollment of certain device types. As such, broad conclusions related to the proportion of IPG/ICD/CRT use are not possible.

Fewer patients were included than initially planned, due to early study closure, making the treatment duration and follow-up for some subjects shorter than intended. To limit over interpretation, in cases where the number of subjects was limited, general observations were avoided. Furthermore, bias may have been introduced because of missing data. Whenever substantial data were missing, it was duly reported in the CRF and interpreted with caution. No adjustments were made for multiple comparisons, but the data were provided with P-values to enable the reader to interpret the clinical and statistical significance of the results.

5 | CONCLUSIONS

PANORAMA 2 provides exhaustive, descriptive data on patients implanted with Medtronic CRM devices from several worldwide geographies, some of which are underreported in literature (e.g., Asia, the Middle East, Eastern Europe, and South Africa). The current study may aid in the interpretation and application of findings from other

CRM studies. Significant variations were found in patient's characteristics, device type selection, and implantation practices across the regions. Some of these differences may reflect larger ethnic, cultural, or socioeconomic variations, while others may be the result of regional guidelines and practice preferences.[36] As some of the regions are experiencing rapid socioeconomic change, future observational trials may be useful to characterize the development of CRM device therapy use.

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CONFLICT OF INTEREST

Bärbel Maus currently holds stock in Medtronic and she is an employee of Medtronic plc. Koen J.P. Verhees is an employee of Medtronic plc. Dr. Naik receives honoraria from Medtronic for conducting clinical research. Other authors: None to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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