

Permanent pacemaker implantation by ethnicity. Are South Asians less susceptible to cardiac bradyarrhythmias compared to Caucasians?

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ABSTRACT

Background

Ethnic variations exist in the incidence and prevalence of coronary artery disease. Observational studies have reported lower rates of sick sinus syndrome in African American patients, compared to Caucasians. Whether similar differences exist among ethnic groups in other geographic settings is unknown.

Aim

To determine rates of permanent pacemaker (PPM) implantation, and of recorded sinus node disease (SND) and atrio-ventricular block (AVB), in Caucasians and South Asians in Leicestershire, United Kingdom (UK).

Methods

We carried out a retrospective cohort study into new PPM implantation during the period 01 May 2006 - 31 March 2014, in patients of South Asian and Caucasian ethnicity resident in Leicestershire, UK. Numbers of individuals at risk in each ethnic group were derived from UK National Census data of 2011. Crude, and age-standardized incidence rates and risk ratios per thousand population of PPM implantation were calculated for Caucasians and South Asians.

Results

During the study period, 4883 patients of the Leicestershire population of 980,328 underwent PPM implantation, a cumulative incidence of 4.98/1000 population. The population cumulative incidence of PPM implantation for SND was 1.74/1000, AVB 2.83/1000, and other indications 0.38/1000 population. These indications were not mutually exclusive. The crude incidence in Caucasians (6.15/1000 population) was higher than in South Asians (1.07/1000 population) and remained higher after age-standardization (5.60/1000 versus 2.03/1000). The age-standardized cumulative incidence of PPM implantation for SND was 1.97/1000 in Caucasians compared to 0.53/1000 in South Asians, and for AVB 3.17/1000 in Caucasians and 1.30/1000 in South Asians. Standardized risk ratios (95% confidence interval) for PPM implantation in Caucasians compared to South Asians for all pacing indications, SND and AVB were 2.70 (2.68-2.71), 3.66 (3.62-3.70), and 2.43 (2.40-2.44) respectively.

Conclusions

Rates of PPM implantation are lower in South Asians residing in the UK, compared to Caucasians. This observation raises the possibility of lower inherent susceptibility to bradyarrhythmias in South Asians compared to Caucasians. Studies aimed at identifying underlying mechanisms, including possible genetic differences, are warranted.

Key words: Pacemaker; ethnicity; sinus node disease; atrioventricular block; direct standardization.

INTRODUCTION

The last decade has seen a marked increase in the number of permanent pacemaker (PPM) implantations, with the average rate in the developed world now more than 700 new implants per million inhabitants per year (1-4). The commonest indications for PPM implantation are sinus node dysfunction (SND) and atrioventricular block (AVB) (3). Sinus node disease can present electrocardiographically as persistent, inappropriate sinus bradycardia, sinus pauses or arrests, sino-atrial exit block, chronotropic incompetence or tachycardia-bradycardia syndrome. Atrioventricular block usually presents progressively as first degree, second degree (Mobitz I, Mobitz II), other higher degree (2:1, 3:1 etc) AVB, and third degree (complete heart block) AVB (1, 5-7). While PPM implantation for all degrees of heart block may have symptomatic benefit, implantation in the context of Mobitz II, other higher degree AVB, and third degree heart block also has survival benefit (1, 6). On this background, European (1) and American (6) guideline indicate that PPM devices should be implanted for lower degree AVB and SND only if symptomatic. On this basis, the number of new PPM implants should equate closely to the incidence of clinically significant SND and AVB.

Ethnicity is an important factor in terms of risk for cardiovascular and cerebrovascular diseases. Compared to Caucasians, people of South Asians ethnicity (India, Pakistan, Bangladesh, Sri Lanka) have increased incidence of coronary artery and cerebrovascular disease (8-15). People of Afro-Caribbean / African ethnicity in the United Kingdom have higher incidence of cerebrovascular, peripheral vascular, and chronic kidney diseases, with lower rates of coronary artery disease (10, 11), while in North America African Americans have higher rates of cardiovascular disease compared to people of White ethnic background (16-18). People of East Asian ethnic origin (China, Japan, Korea, Taiwan) have lower coronary artery disease, and higher cerebrovascular disease, rates (17, 19). Finally, in North America, Hispanics have lower cardiovascular mortality despite higher prevalence of risk factors (17, 20, 21).

While differences in the major ethnic groups living in geographic regions will lead to different inter-ethnic comparisons, these observations suggest strongly that there are indeed ethnic differences in susceptibility to cardiovascular and cerebrovascular diseases. Possible contributory factors include differences in cardiovascular risk factors (8, 12, 20), socio-economic differences among ethnic groups (22-24), and possible ethnic disparities in genetic susceptibility for the various cardiovascular diseases (15, 23).

Age is the most significant risk factor for bradyarrhythmias, with age-related idiopathic fibrotic degeneration of cardiac conductive tissue and ischaemic heart disease topping the list of aetiologies (1, 6). The epidemiology of SND and AVB are poorly described. The incidence of SND is estimated at 0.8/1000 person-years in USA (25), where PPM implantation rates following admission with complete heart block were lower in African-Americans and other ethnic minorities compared to Caucasians, differences which were only partly explained by ethnic variation in access to health insurance cover (26). Recent data derived from two combined large, prospective cohort studies in the USA suggested ethnicity as a risk factor of SND with a lower risk in African Americans compared to Caucasians (25). Whether other ethnic groups have different risk profiles for SND or AVB compared to Caucasians remains unknown.

Individuals of South Asians ethnic origin make up the largest minority ethnic group in the United Kingdom (UK), approximately 4.9 % of the total population (27). In the county of Leicestershire, individuals of South Asian ethnicity constitute approximately 15% of the population. We have reported higher incidence rates of coronary artery disease (28) and heart failure (29, 30) in the local South Asian population compared to Caucasian patients, but similar case-fatality (28, 29). We aimed to determine the association of ethnicity with bradyarrhythmia risk, by comparing the incidence of PPM implantation in Caucasians and South Asians in this UK population with a high density of individuals of South Asian ethnicity. We compared the indication for PPM implantation, a surrogate for the true incidence of SND or AVB, in each ethnic group.

METHODS

Study design and population: We carried out a retrospective cohort study into cumulative PPM implantation at the University Hospitals of Leicester between May 1st 2006 and March 31st 2014.

The population at risk (the exposed population) was the population of Leicestershire. Data regarding the population at risk were obtained from the UK National Census of 2011, obtained via the Office for National Statistics (31). The 2011 Census was carried out at the midpoint of our study period and was thus likely to provide an accurate assessment of the size of the population at risk and of the study population, ie numbers of individuals of Caucasian and of South Asian ethnic background.

The study population constituted patients of Caucasian or South Asian ethnicity, local recording of which is thorough. Given small numbers of patients, and of PPM implantations, in other ethnic groups (Afro-Caribbean, other Africans, East Asians, Arabs, and others), these were not considered in this analysis. We excluded patients with previous PPM implantation who attended for a generator change or lead repositioning or replacement.

Patients with PPM who attended for device upgrades were also excluded as were those whose indication for PPM implantation was AV node ablation for refractory atrial arrhythmias. Only patients undergoing new PPM implantation for bradyarrhythmia were retained for the study. The UK total population from the 2011 census was used as the population for direct standardization.

Exposure and outcome measures: The exposure of interest was Caucasian and South Asian ethnicity and the outcome event was incidence rates of PPM implantation.

Statistical analysis: Crude and age-specific cumulative incidence PPM implantation rates per thousand population were calculated for Caucasians and South Asians. Each patient was categorised into one of four age groups; < 25 years, 25-49 years, 50-74 years, and ≥ 75 years. Attempts to categorize into smaller age bands were hampered by small numbers, or the absence of, implantation events in some age bands. In calculating the incidence, the numerator consisted of PPM first implants for each ethnic group, in total and by age group, while the denominator was the respective population from the 2011 census. In view of differences in age structure of the Caucasian and South Asian populations (Caucasians were on average older), PPM implantation rates were directly standardised using the UK general population from the 2011 census. Age-specific crude PPM implantation cumulative incidence rates for each ethnic group were applied to the population within each age group (< 25 years, 25-49 years, 50-74 years, and ≥ 75 years) of the total UK population to obtain the age-specific expected events. The total number of expected events (age-standardized events) for each ethnic group was obtained by summing the age-specific events. After applying the age-specific crude cumulative incidences for each ethnic group to the UK population and obtaining the expected number of PPM implants, we calculated the age-adjusted incidence per 1000 population. Crude and age-standardized risk ratios of PPM implantation for Caucasians compared to South Asians were calculated. Subgroup analyses for sinus node disease and atrio-ventricular node disease were also carried out. Analysis were performed using STATA 11.

RESULTS

Patient characteristics

During the study period, from a Leicestershire population of 980,328 individuals, 4883 patients received a first PPM for bradycardia. After exclusion of other minority ethnic groups (n=37), a total of 4846 first implants were retained for the study, of which 4679 (96.55%) were Caucasians and 167 (3.45%) were South Asians (Figure 1).

Table 1 shows the demographic characteristics of patients who underwent PPM implantation, stratified by Caucasian/South Asian ethnicity. Caucasians were older and had a higher rate of atrial fibrillation & atrial flutter compared to South Asians. A higher proportion of implants in South Asians were performed as non-elective procedures.

Cumulative incidence of permanent pacemaker implantation for the total population

The overall PPM implantation incidence for the population at risk was 4.98/1000 inhabitants. The incidence of PPM implantation for SND was 1.74/1000, AVB 2.83/1000, and other indications 0.38/1000 population. These indications were not mutually exclusive.

Crude and age-adjusted cumulative incidence rates of PPM implantation by ethnicity

Table 2 shows 2011 census results for Leicestershire by ethnic group and age groups and the total UK national population. Most importantly, it also shows crude and age-adjusted incidence rates of PPM implantation by ethnicity for any pacing indication (sinus node dysfunction, atrio-ventricular block, other). The crude rate in Caucasians (6.15/1000 population) was higher than in South Asians (1.07/1000) and remained higher after age-standardization (5.60/1000 versus 2.03/1000 in Caucasian and South Asian respectively). A similar pattern was seen in subgroup analyses for SND (**Table 3**) and for AVB (**Table 4**). The age-standardized incidence rates of PPM implantation for SND was 1.97/1000 in Caucasians compared to 0.53/1000 in South Asians, while corresponding, age-standardized rates for AVB were 3.17/1000 and 1.30/1000 respectively.

Incidence risk ratios

Table 5 shows crude and age-standardized risk ratios of PPM implantation in Caucasians compared to South Asians. Compared to South Asians, the standardised risk-ratio for Caucasians was 2.70 (95% CI 2.68-2.71). Similar patterns were evident for implantation for the indications of SND and AVB.

DISCUSSION

To the best of our knowledge, this is the first study to report differences in PPM implantation rates between Caucasians and South Asians. We observed an age-standardised

first PPM implantation rate which was 2.7 times higher in Caucasian, compared to South Asian patients. This finding was consistent when considering the indication for device implantation, SND or AVB. As rates of PPM implantation are likely to be good surrogate for rates of clinically significant bradyarrhythmias, our data suggest that these conditions are much less common in South Asian patients in the UK, compared to the Caucasian population.

Individuals of South Asian origin constitute the single largest ethnic minority group in the UK, approximately 5% of the UK population (27). In Leicestershire, South Asians constitute a much higher proportion of the population, 15.8% based upon 2011 Census figures. In this context, the Leicestershire population is one in which ethnic differences in the epidemiology of individual disease states can be assessed with greater robustness than is possible in other areas. In this setting, our data indicating lower rates of PPM implantation in South Asian patients are likely to be reliable.

Age is the most important risk factor for cardiac conductive disease (1, 6). Our results suggest that the overall incidence of clinically significant SND and AVB are 1.74 and 2.83/1000 population respectively. In the context of an older patient population, crude rates of PPM implantation were higher in Whites compared to South Asians. However, after age standardization, implant rates remained approximately 2.7 times greater in Caucasians, a phenomenon which was apparent in patients receiving PPM for SND and in those in whom the indication was AVB.

It has been reported that African American men are less likely to be hospitalised for SND than white men (31). A recent publication using combined data from two large prospective cohort studies in the USA suggested ethnic differences in the risk of sick sinus syndrome, with African Americans having a 41 % relative risk reduction compared to whites (25). On this background, our observations support the notion of higher risk of cardiac bradyarrhythmias in Caucasians compared to other ethnic groups.

There are a number of possible explanations for our observations. Firstly, ascertainment bias, leading to under-diagnosis of cases of bradyarrhythmia in South Asian patients, either through poor access to, or underuse of, health services. Factors contributing to poor health access in ethnic minorities include linguistic barriers, level of literacy, and cultural beliefs (32). Data from the USA suggest socioeconomic issues contribute to differences in rates of PPM implantation in African Americans and other ethnic minority groups compared to Caucasians (26). However, data have shown equitable access to health care services and similar health seeking behaviours in South Asians compared to Caucasians in the UK (33, 34). Moreover, given the free access to the National Health Service in the UK, we feel it is highly unlikely that poor or restricted access to health care could account for the relatively very low PPM implantation rates in our South Asian patients.

Secondly, there could be a problem of under-treatment, or differential implantation of PPM, by clinicians influenced by the ethnic origin of the patient. We feel this is unlikely; studies utilising data from U.K. national registries indicate equitable provision of medical treatment and procedures for cardiovascular diseases for South Asians and White Europeans in the UK (12, 35, 36). We suggest that there may be real, possibly genetically determined, differences among ethnic groups in terms of the propensity to sinus node dysfunction and atrioventricular block.

Our novel observation of apparent differences between ethnic groups in the risk of clinically meaningful cardiac bradyarrhythmias should be considered in the context of well recognised ethnic variation in the risk of other cardiovascular pathologies. South Asians have higher prevalence of coronary artery, cerebrovascular and chronic kidney diseases compared to Caucasians (8-11, 15, 19, 37). However, while the incidence of these conditions is higher, outcomes are comparable, or perhaps better in South Asians (12, 13). Blacks have increased rates of hypertension, diabetes, morbidity and mortality from strokes and chronic kidney disease compared to Caucasians. In the UK, Blacks have a significantly lower incidence and mortality from coronary artery disease compared to Caucasians (10, 11), while in the USA, rates are higher in African Americans (17, 37). Mortality from heart diseases are lower in Chinese, Japanese, Koreans, but mortality from cerebrovascular diseases higher, compared to Caucasians (11, 14). The incidence and prevalence of atrial fibrillation is higher in Caucasians when compared to other ethnic groups, even when ascertainment bias has been overcome, suggesting lower susceptibility to AF in non-White ethnic groups (38-40). Peripheral vascular disease incidence and prevalence are higher in African Americans compared to non-Hispanic Whites in the USA (16, 18), while rates are lower in South Asians, East Asians, and Hispanics compared to Caucasians (41, 42). Finally, despite higher cardiovascular risk in Hispanics, the rate of cardiovascular mortality is significantly lower when compared to non-Hispanic Whites (20, 21).

Much of the information pertaining to variability in the susceptibility to cardiovascular disease among ethnic groups comes from the USA, where inequalities in the provision of cardiovascular care remain prevalent (22) and may contribute to the observations. However ethnic differences in rates of cardiovascular disease may reflect genetic variations in that particular disease, ethnic disparities in cardiovascular risk factors, socio-economic differences, or a combination of factors (23). Closing the socio-economic gap, improving access to evidence-based health care, and optimizing control of risk factors in the higher prevalent ethnic groups remain the key systemic measures. Genetic studies are likely to open new therapeutic windows and therefore should be proactively encouraged.

LIMITATIONS

Our data from a single centre may not be generalizable to South Asian patients in other areas of the UK. However significant variance from our observations are unlikely, given the uniform provision of National Health Service provision across the country. We were unable to explore PPM implantation rates in ethnic minority groups other than South Asian, in view of very small numbers in our population. We are unable to discount ethnic differences in seeking and accessing health care health, particularly among elderly South Asian individuals. However our data showed that the difference in implant rates were apparent across all age strata. Finally although the incidence of PPM implantation is likely to reflect the incidence of clinically significant SND and AVND, this is a surrogate for the true incidence of SND or AVND. Our study did not identify asymptomatic SND and lower degree AVN disease. Finally, residual confounding remains a possibility as the main results of this study were only age-standardized.

CONCLUSIONS

The rate of permanent pacemaker implantation is lower in South Asians residing in the UK, compared to Caucasians. In the setting of equitable access to health care, our observations raise the possibility of lower, potentially genetic, susceptibility to bradyarrhythmias in South Asians. Future studies aimed at identifying any underlying driving genetic markers are warranted.

Figure 1: Flow chat of study population for permanent pacemaker implantation University Hospitals of Leicester May 2006 to March 2014.

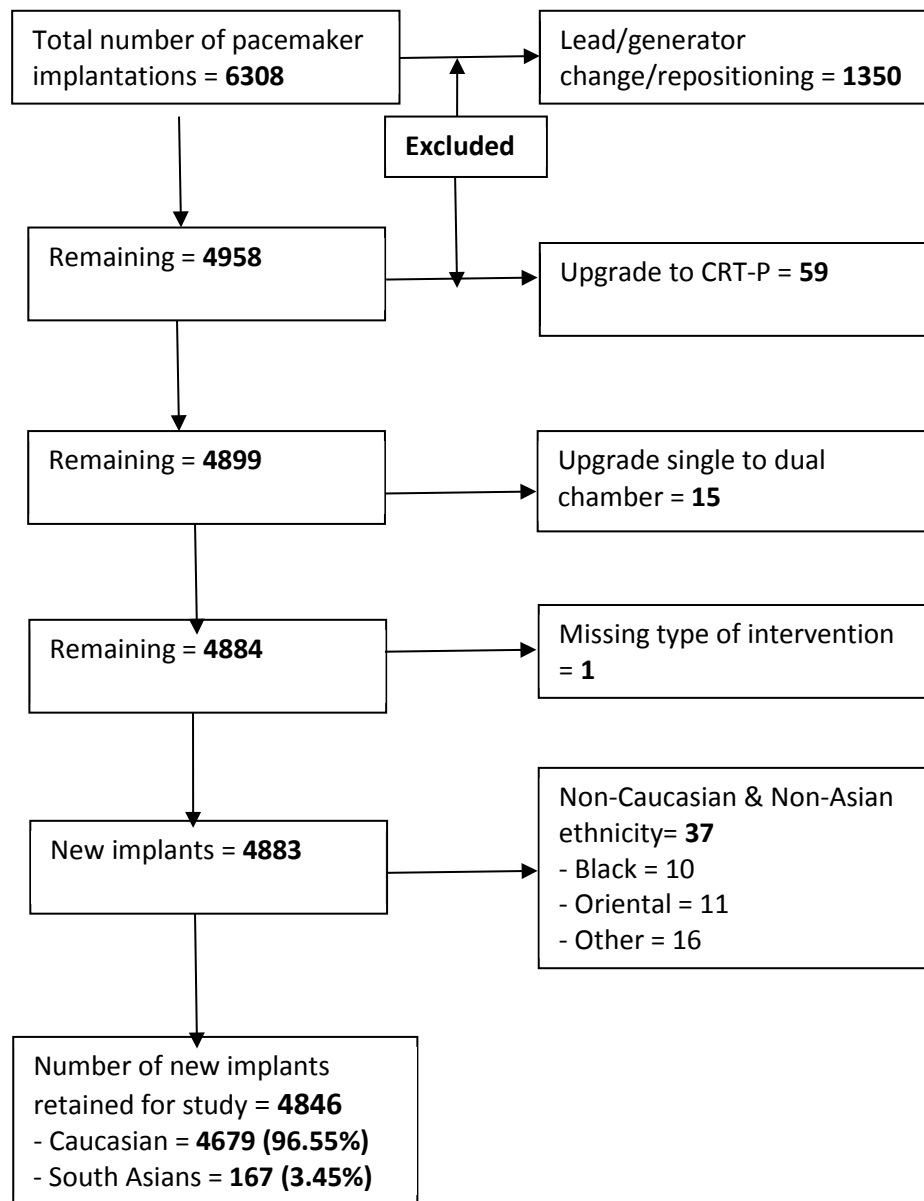


Table 1: Characteristics of patients undergoing permanent pacemaker implantation by ethnicity.

		All	Caucasians	South Asians	P value
<i>Number</i>		4846	4679 (96.55%)	167 (3.45%)	
Age (mean (SD))		74.96 (14.37)	75.12 (14.32)	70.45 (14.90)	<0.001
Gender (male)		2915 (60.17)	2819 (60.26%)	96 (57.49%)	= 0.472
Main symptoms	Syncope	1872 (38.65%)	1811 (38.73%)	61 (36.53%)	= 0.566
	Presyncope	1725 (35.62%)	1668 (35.67%)	57 (34.13%)	= 0.683
	Dyspnoea	542 (11.19%)	515 (11.01%)	27 (16.17%)	= 0.038
AF/Atrial flutter		915 (18.88%)	903 (19.30%)	12 (7.19%)	<0.001
Indication	SND	1696 (35.00%)	1648 (35.22%)	48 (28.74%)	= 0.101
	AVB	2758 (56.91%)	2655 (56.74%)	103 (61.68%)	=0.150
	Other	365 (7.53%)	353 (7.54%)	12 (7.19%)	=0.240
	Unknown	67 (1.38%)	63 (1.35%)	4 (2.40%)	= 0.322
Dual chamber PPM		2753 (56.90%)	2646 (56.65%)	107 (64.07%)	= 0.057
Urgency	Elective	2427 (50.08%)	2359 (50.42%)	68 (40.72%)	= 0.014
	Urgent	2367 (48.84%)	2272 (48.56%)	95 (56.01%)	= 0.034
	Emergency	52 (1.07%)	48 (1.03)	4 (2.40%)	= 0.091

SND = Sinus node dysfunction; AVB = Atrioventricular block; 40 patients had both SND and AVB.

Table 2: Crude cumulative incidence rates and age-standardized rates of permanent pacemaker implantation in Leicestershire May 2006 to March 2014 for all indications

Table 2A: Crude cumulative incidence rates of permanent pacemaker implantation						
Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Caucasian population in Leicestershire census 2011	Number of PPM	Incidence (per 1000) of PPM implantation	Asian population in Leicestershire census 2011	Number of PPM	Incidence rate (per 1000) of PPM implantation
< 25 years	226231	86	0.38	58116	4	0.07
25-49 years	248517	132	0.53	59837	6	0.10
50-74 years	220471	1509	6.84	33002	79	2.30
≥ 75 years	66184	2952	44.60	4545	78	17.16
Total	761403	4679	-	155500	167	-
Crude incidence rate	-	-	4679/761403 = 6.15 ‰	-	-	167/155500 = 1.07 ‰

Table 2B: Direct standardization cumulative incidence rates of permanent pacemaker implantation						
Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Standard UK population Census 2011	Age-specific PPM incidence rates (per 1000)	Expected number of PPM cases in standard UK population	Standard UK population Census 2011	Age-specific PPM incidence rates (per 1000)	Expected number of PPM cases in standard UK population
< 25 years	19395000	0.38	7370.1	19395000	0.07	1338.3
25-49 years	21896000	0.53	11626.8	21896000	0.10	2189.6
50-74 years	16996000	6.84	116320.6	16996000	2.30	40688.4
≥ 75 years	4896000	44.60	218376.3	4896000	17.16	84025.2
Total	63183000	-	353693.8	63183000	-	128241.5
Standardized incidence rates	-	353694.8/63183000 = 5.60 ‰	-	-	128241.5/63183000 = 2.03 ‰	-

PPM=Permanent Pacemaker; ‰=per thousand

Table 3: Crude cumulative incidence rates and direct standardization rate of permanent implantation in Leicestershire May 2006 to March 2014 for sinus node dysfunction (SND).

Table 3A: Crude cumulative incidence rates of permanent pacemaker implantation

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Caucasian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation	Asian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation
< 25 years	226231	21	0.09	58116	1	0.02
25-49 years	248517	58	0.23	59837	2	0.03
50-74 years	220471	579	2.63	33002	28	0.85
≥ 75 years	66184	990	14.96	4545	17	3.74
Total	761403	1648	-	155500	48	-
Crude incidence rate	-	-	1648/761403 = 2.16 ‰	-	-	48/155500 = 0.31 ‰

Table 3B: Direct cumulative standardization incidence rates of permanent pacemaker implantation

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Standard UK population Census 2011	Age-specific PPM incidence rates (per 1000)	Expected number of PPM cases in standard UK population	Standard UK population Census 2011	Age-specific PPM incidence rates (per 1000)	Expected number of PPM cases in standard UK population
< 25 years	19395000	0.09	1799.9	19395000	0.02	333.6
25-49 years	21896000	0.23	5110.5	21896000	0.03	732.8
50-74 years	16996000	2.63	44634.9	16996000	0.85	14419.4
≥ 75 years	4896000	14.96	73235.8	4896000	3.74	18312.9
Total	63183000	-	124781.1	63183000	-	33797.7
Standardized incidence rates	-	124781.1/63183000 = 1.97 ‰	-	-	33797.7/63183000 = 0.53 ‰	-

PPM=Permanent Pacemaker; ‰=per thousand

Table 4: Crude cumulative incidence rates and direct standardization rate of permanent implantation in Leicestershire May 2006 to March 2014 for atrioventricular block (AVB).

Table 4A: Crude incidence rates of permanent pacemaker implantation

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Caucasian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation	Asian population in Leicestershire census 2011	Number of PPM	Incidence rate of PPM implantation
< 25 years	226231	59	0.26	58116	3	0.05
25-49 years	248517	63	0.25	59837	3	0.05
50-74 years	220471	776	3.52	33002	44	1.33
≥ 75 years	66184	1757	26.55	4545	53	11.66
Total	761403	2655	-	155500	103	-
Crude incidence rate	-	-	2655/761403 = 0.003486 = 3.49 ‰	-	-	103/ 155500 = 0.000662 = 0.66 ‰

Table 4B: Direct standardization cumulative incidence rates of permanent pacemaker implantation

Age group	<i>Caucasians</i>			<i>South Asians</i>		
	Standard UK population Census 2011	Age-specific PPM incidence rates (per 1000)	Expected number of PPM cases in standard UK population	Standard UK population Census 2011	Age-specific PPM incidence rates (per 1000)	Expected number of PPM cases in standard UK population
< 25 years	19395000	0.26	5056.3	19395000	0.05	1000.8
25-49 years	21896000	0.25	5550.6	21896000	0.05	1096.9
50-74 years	16996000	3.52	59820.8	16996000	1.33	22660.8
≥ 75 years	4896000	26.55	129974.1	4896000	11.66	57092.7
Total	63183000	-	200401.8	63183000	-	81851.2
Standardized incidence rates	-	200401.8/ 63183000 = 3.17 ‰	-	-	818551.2/ 63183000 = 1.30 ‰	-

PPM=Permanent Pacemaker; ‰=per thousand

Table 5: Crude and age-standardized (direct) risk ratios (95% CI) of permanent pacemaker implantation for Caucasians compared to South Asians, May 2006 to March 2014.

	Crude risk ratios	P value	Age-standardized risk ratios	P value
All indications	5.72 (4.99-6.56)	<0.0001	2.70 (2.68-2.71)	< 0.0001
Sinus node dysfunction	7.01 (5.48-8.97)	< 0.0001	3.66 (3.62-3.70)	< 0.0001
Atrioventricular block	5.26 (4.42-6.28)	< 0.0001	2.42 (2.40-2.44)	< 0.0001

Above are risk ratios and 95% confidence intervals

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