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Representation of people of South Asian origin in cardiovascular outcome trials of glucose-lowering therapies in Type 2 diabetes

Short title: Representation of South Asian people in cardiovascular outcome trials

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What's new?

- This appears to be the first time that the representation of people of South Asian origin within major clinical trials in diabetes has been systematically and quantitatively appraised.
- The findings not only have implications for necessary caution in the broad application of results from major clinical trials, but also point to a need for further improvement in the recording and reporting of ethnicity and in ensuring representative ethnic balance in trial recruitment.

Abstract

Aims Our aim was to investigate the proportional representation of people of South Asian origin in cardiovascular outcome trials of glucose-lowering drugs or strategies in Type 2 diabetes, noting that these are among the most significant pieces of evidence used to formulate the guidelines on which clinical practice is largely based.

Methods We searched for cardiovascular outcome trials in Type 2 diabetes published before January 2015, and extracted data on the ethnicity of participants. These were compared against expected values for proportional representation of South Asian individuals, based on population data from the USA, from the UK, and globally.

Results Twelve studies met our inclusion criteria and, of these, eight presented a sufficiently detailed breakdown of participant ethnicity to permit numerical analysis. In general, people of South Asian origin were found to be under-represented in trials compared with UK and global expectations and over-represented compared with US expectations. Among the eight trials for which South Asian representation could be reliably estimated, seven under-represented this group relative to the 11.2% of the UK diabetes population estimated to be

South Asian, with the representation in these trials ranging from 0.0% to 10.0%.

Conclusions Clinicians should exercise caution when generalizing the results of trials to their own practice, with regard to the ethnicity of individuals. Efforts should be made to improve reporting of ethnicity and improve diversity in trial recruitment, although we acknowledge that there are challenges that must be overcome to make this a reality.

Introduction

People of South Asian origin are an important target for the prevention and treatment of diabetes. In the UK, for instance, Type 2 diabetes is about two times more prevalent in this group than in white European people [1]. Furthermore, in the USA, ~ 17.4% of people of South Asian origin have diabetes [2]. The risks of diabetic retinopathy and end-stage renal disease are known to be higher in South Asian people than in the white European population, and individuals of South Asian origin are also known to have a higher mortality rate from coronary heart disease and stroke [1].

There is also some evidence suggesting that there are ethnic differences in response to diabetes therapies. For instance, glucagon-like peptide-1 receptor agonists have been found to lower HbA_{1c} levels to a greater extent in Asian-dominant studies than in non-Asian-dominant studies, perhaps reflecting a different pathophysiology of Type 2 diabetes in different ethnic groups [3].

As in other conditions, clinical practice in Type 2 diabetes is influenced heavily by various guidelines; these, in turn, are informed by clinical trials, with much weight being placed on cardiovascular outcome trials. The applicability of the results from trials to clinical practice is dependent on the representativeness of study participants' demographic characteristics. Studies in both acute and chronic conditions, however, have suggested that non-white ethnic

groups are often under-represented in clinical trials [4–7]. Here, we report on the proportion of participants of South Asian origin recruited to cardiovascular outcome trials of glucose lowering in Type 2 diabetes and explore whether proportional ethnic representation was achieved in these trials.

Methods

To identify relevant studies, we took, as a starting point, Holman *et al.*'s 2014 systematic review of cardiovascular outcome trials of glucose lowering in Type 2 diabetes [8]. We searched PubMed (MEDLINE) to identify additional relevant studies published after the original systematic review, in the period 5 January 2014 to 9 January 2015. In addition to the exclusion criteria from the original review, we also excluded studies that involved randomization during hospitalization in order to focus on trials exploring glucose lowering in the context of general diabetes practice, as opposed to the treatment of acute coronary syndromes.

The abstracts were reviewed by AJ and verified by KK and WH to identify additional relevant studies; these were combined with the studies identified in the Holman *et al.* systematic review [8] to provide the full list of studies to be investigated. The additional exclusion criterion was also applied to the studies identified by Holman *et al.*

The primary publication or baseline data paper for each trial was obtained and the ethnicity data were extracted by AJ using a standard form and verified by JG. Following Bhopal [9], we used a broad set of terms when extracting ethnicity data, including 'Asian Indian', 'Indian', 'Indian Asian' and 'South Asian'. Where relevant, participants were described only as 'Asian' or the geographic location was stated as 'Asia', the number of South Asian participants was estimated as 38.9% of the total number from Asia, based on the United

Nations world population estimates [10].

The calculated percentages for South Asian representation within the trials were compared with the proportion of people with diabetes estimated to be of South Asian origin according to data from three geographic regions: 11.2% for the UK [1], 2.3% for the USA [2,11,12], and 20.6% globally [11]. Comparing the South Asian trial representation with global data provides an illustration of the overall applicability of the study data, while the comparisons with the UK and US diabetes populations provide country-specific examples for regions that have seen different levels of immigration from South Asia.

For statistical analysis, the binomial exact test with two-tailed *P*-values was performed, comparing South Asian representation within the trials with the expected representation for each of the three comparator regions, to explore the likelihood that any differences seen could have occurred by chance if there was no differential recruitment. *P*-values < 0.05 were considered to be significant.

Results

Twenty journal articles were identified by our supplementary literature search, but all were excluded after abstract review (Fig. 1). Of the 14 studies identified in the Holman *et al.* systematic review [8], two –Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) and Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI 2) – were excluded because they involved hospitalized individuals. The 12 remaining studies [13–24] are detailed in Table 1 (including expansions of their acronyms), along with their estimated breakdown with regard to South Asian participants. The nature and reporting of the recruitment of South Asian participants were variable.

When the representation within trials was compared against the proportion of South Asian

people among the diabetes population of the UK, South Asian participants were found to be proportionally under-represented in seven of the eight trials (six trials, $P < 0.001$; UKPDS, $P = 0.02$) and over-represented in ADVANCE ($P < 0.001$).

From a US perspective, VADT appears to have proportionally represented South Asian individuals ($P = 0.368$); however, this is based upon the debatable assumption that anyone in the trial who was not non-Hispanic white, Hispanic white or black was Asian. By our means of analysis, all other studies were deemed to have over-represented people of South Asian origin when considering the US population with diabetes, except Look AHEAD and ACCORD, which under-represented people of South Asian origin (all $P < 0.001$).

From a global perspective, all eight trials that were numerically analysed were found to have proportionally under-represented South Asian participants compared with the expected proportion estimate (all $P < 0.001$).

Finally, none of the identified trials reported outcomes separately according to ethnicity; however, one UKPDS publication investigated the characteristics of people of different ethnic origins at diagnosis of diabetes in the study population [25].

Discussion

A lack of proportional representation in trials is of particular significance in conditions for which ethnicity may have an impact on outcomes, as is thought to be the case for Type 2 diabetes. In general, our analysis of cardiovascular outcome trials of glucose-lowering therapies shows under-representation of South Asian participants in trials when compared against the UK and global diabetes populations, and over-representation when compared with the US population.

Another finding, and one that represents a limitation of our analysis, is that the reporting of

ethnicity within published trial reports was not optimal, with several papers failing to provide a breakdown that included Asian or South Asian categories. (In our analysis, several of the key values in Table 1 had to be derived by estimation.) Reporting standards in the area of ethnic breakdowns could be improved significantly.

A further consideration is that, even where the values are accurate, the trial populations may not truly represent the global, UK or US populations of South Asian origin, as this group is in turn made up of a number of subpopulations, and the ratios in the trials may be different from those in clinical practice.

We acknowledge that no clinical trial is likely to be truly 'global' in scope with study sites in all countries of the world. Nevertheless, there is a growing desire for inclusion of a more diverse population in clinical trials [5,26]. In the USA, for instance, the lack of proportional representation in studies funded by the National Institutes of Health (NIH) was highlighted by the NIH Revitalization Act of 1993, which mandated the appropriate inclusion of minority ethnic groups in research projects supported by the body [27]. A federal Executive Order in 2009 [28] has further contributed to an increased research focus on Asian Americans. However, there remains a lack of global guidance relating to the issue of proportional representation.

For greater diversity in the populations recruited for trials to become a reality, a number of barriers needs to be overcome (with a potential role existing for researchers in the UK, for instance, supporting researchers in South Asia) [5]. As an example, new recruitment strategies and enhanced logistical support will be required to provide researchers with information about different ethnic groups and to ensure that engagement is both culturally appropriate and sustainable [5]. This might include developing translated materials related to the trial and the use of interpreters to ensure that participants fully understand what participation entails. The Prevention of Diabetes and Obesity in South Asians (PODOSA)

trial investigators reported on their experiences of recruiting South Asian people to participate in their trial and suggested that a community-orientated, personal approach was most successful [29]. The importance of health literacy, general literacy and numeracy in this process should not be underestimated.

We propose that clinicians across the world exercise caution in generalizing the results of trials to their own practice, with regard to individuals' ethnicity. We also call for improved diversity in trial recruitment, while acknowledging that there are challenges that must be overcome in order to make this a reality. Finally, we recommend developing an evidence base that highlights where there is a clinical imperative for tailored strategies for different ethnic groups, with potentially significant benefits for the populations concerned and also for healthcare economies.

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Competing interests

KK has received funds for research from, acted as consultant to or received honoraria from Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Takeda and Unilever. SB has received educational grants and consultation and speaker fees from AstraZeneca, Janssen, Lilly, MSD, Novo Nordisk and Sanofi. He has received research funds for investigator-initiated trials from Novo Nordisk. MAK has received educational grants or speaker fees from, and performed consultancy services for Novo Nordisk, Janssen,

Lilly, AstraZeneca, MSD, Roche, Boehringer Ingelheim and Sanofi. KP has no conflicts to declare in the past 12 months. VP has acted as consultant to, or received honoraria from Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk and Sanofi-Aventis. AJ, PS and JG have no conflicts of interest to disclose. WH has received educational grants, research grants or speaker fees from, and performed consultancy services for Novo Nordisk, Allianz, Novartis, Janssen, AstraZeneca, MSD and Sanofi.

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FIGURE 1 Flow chart illustrating the process used to identify studies included in the analysis.

Table 1 Representation of South Asian participants included in cardiovascular outcome trials of glucose lowering in Type 2 diabetes

Study	Year of primary publication	*N*	Ethnicity demographics relating to South Asian participants		Proportion of participants estimated to be of South Asian origin, and comparison with proportion of South Asian individuals in global, US and UK diabetes populations			
			Descriptor	Proportion of trial population (%, *n*)	Estimated representation of South Asian trial participants [†] (%, *n*)	Difference from expected global representation (%)	Difference from expected US representation (%)	Difference from expected UK representation
UKPDS [13]	1998	3 867	Indian Asian	10 (387)	**10.0** (387)	–10.6*	+7.7*	–1.2**
ProACTIVE [14]	2005	5 238	Non-white	1.4 (74)	Could not be reliably estimated	–	–	–
ACCORD [15]	2008	10 251	Non-white	0 (0)	**0** (0)	–20.6*	–2.3*	–11.2*
ADVANCE [16]	2008	11 140	Asia	37.1 (4136)	**14.4** (1608)	–6.2*	+12.1*	+3.2*
HEART2D [17]	2009	1 115	India	6.3 (70)	**6.3** (70)	–14.3*	+4.0*	–4.9*
VADT [18]	2009	1 791	Not white (Hispanic or non-	5.0 (90)	**2.0** (35)	–18.6*	–0.3***	–9.2*

			Hispanic) or black					
RECORD [19]	2009	4 447	Not white	1.1 (48)	Could not be reliably estimated	–	–	–
ADDITION-Europe [20]	2011	2 941	Not white	5.3 (156)	Could not be reliably estimated	–	–	–
ORIGIN [21]	2012	12 612	India	3.1 (390)	**3.1** (390)	–17.5*	+0.8*	–8.1*
SAVOR-TIMI 53 [22]	2013	16 492	Other (not white or Hispanic)	3.3 (544)	Could not be reliably estimated	–	–	–
EXAMINE [23]	2013	5 380	Asian	20.2 (1089)	**7.9** (423)	–12.7*	+5.6*	–3.3*
Look AHEAD [24]	2013	5 145	Asian or Pacific Islander	1.0 (50)	**0.4** (19)	–20.2*	–1.9*	–10.8*

*$P < 0.001$; **$P = 0.02$; ***$P = 0.368$.

†If a broad Asian category was presented, the proportion of South Asians was determined as 0.389 × actual Asia/Asian population (this was a conservative estimate – with regard to testing for under-representation of South Asian participants – in the case of Look AHEAD, for which the ethnic descriptor included Pacific Islanders).

ACCORD, Action to Control Cardiovascular Risk Diabetes trial; ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; HEART2D, Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus; Look AHEAD, Look Action for Health in Diabetes; ORIGIN, Outcome Reduction with an Initial Glargine

Intervention; ProACTIVE, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; SAVOR-TIMI, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.