

Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine

Sarah E McDowell, Jamie J Coleman, R E Ferner

Abstract

Objective To review the evidence for ethnic differences in susceptibility to adverse drug reactions (ADRs) to cardiovascular drugs.

Design Systematic review and meta-analysis.

Data sources We searched Medline and Embase to March 2005. Reference lists of identified articles were hand searched for further relevant articles.

Review methods Studies were eligible for inclusion if they included at least two ethnic groups and one or more ADRs. We excluded case reports and case series.

Results 564 studies contained some description of ethnicity and an ADR, and 132 of them related to cardiovascular therapies. Twenty four studies provided data for ADRs for at least two ethnic groups and were therefore eligible for inclusion. In pooled analyses the relative risk of angio-oedema from angiotensin converting enzyme (ACE) inhibitors in black compared with non-black patients was 3.0 (95% confidence interval 2.5 to 3.7); the relative risk of cough from ACE inhibitors was 2.7 (1.6 to 4.5) in East Asian compared with white patients; and the relative risk of intracranial haemorrhage with thrombolytic therapy was 1.5 (1.2 to 1.9) in black compared with non-black patients.

Conclusion Patients from different ethnic groups have different risks for important ADRs to cardiovascular drugs. Ethnic group may therefore be one determinant of harms of a given treatment in the individual patient, either because it acts as a surrogate measure of genetic make up or because cultural factors alter the risk. Data are sparse, and regulators should consider asking for better data before licensing.

Introduction

Adverse drug reactions (ADRs) cause considerable morbidity and mortality and account for about 6.5% of acute hospital admissions.¹⁻² Genetic make up, age, sex, physiological changes, exogenous factors such as coprescribed drugs or diet, and disease state can all alter a patient's susceptibility to ADRs.³⁻⁶

There is no consensus on the relation between genetics and ethnic or racial classifications.⁷⁻¹³ Some have argued that ethnic and racial labels are poor bio-

logical proxies for underlying genotype,⁸⁻¹² but ethnic classification could still account for complex interactions between genetics, environment, society, and other factors.¹⁰ Some drugs have been shown to be more effective in certain ethnic groups¹⁴⁻¹⁵ and isosorbide dinitrate plus hydralazine (BiDil) has been recently licensed in the United States specifically for use in black patients.¹⁶

It is not known to what extent susceptibility to ADRs might depend on ethnic group, whether as a result of genetic or cultural factors. We therefore undertook a systematic review of reported associations between increased susceptibility and ethnicity.

Methods

Search strategy

In March 2005 we searched Medline (from 1951) and Embase (from 1974), without any language restriction, excluding case reports or case series (see appendix 1 on bmj.com).

Selection of studies

Two reviewers (JJC and SEMcD) independently reviewed the title and abstract of all identified studies. A third reviewer (REF) examined studies initially identified for inclusion. Studies selected by any two reviewers were retained and the relevant drug was classified using the *British National Formulary* (No 49).¹⁷ We obtained full text copies of studies referring to cardiovascular drugs. We included studies if they contained data comparing at least two ethnic groups for a specified ADR. We hand searched included studies to identify further relevant research and approached the authors of studies that suggested they might have relevant data not included in the published papers.

We assessed each study for selection bias, performance bias, attrition bias, and detection bias.¹⁸

Editorial by Eliasson

West Midlands
Centre for Adverse
Drug Reaction
Reporting, City
Hospital,
Birmingham
B18 7QH

Sarah E McDowell
research officer
R E Ferner
director

Department of
Clinical
Pharmacology,
University of
Birmingham,
Birmingham
B15 2TH

Jamie J Coleman
specialist registrar in
clinical pharmacology

Correspondence to:
R E Ferner
r.e.ferner@bham.ac.uk

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References to included trial (w1-w24), details of the search strategy, the data extraction form, and classification of ethnicity can be found on bmj.com.

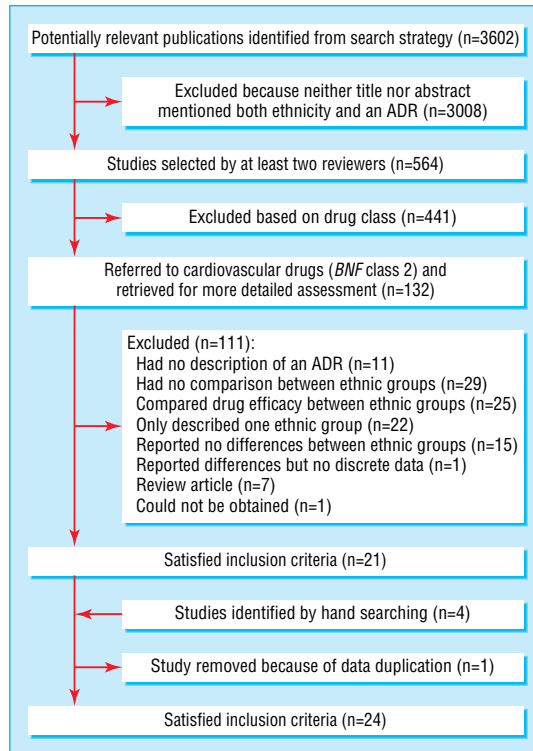


Fig 1 Flow chart of study selection

Data analysis

We used a standard form to extract data for analysis (see appendix 2 on bmj.com). Terms to describe ethnicity varied widely and to present the data using consistent terminology we used the terms black, East Asian, South Asian, and white¹⁹ (see appendix 3 on bmj.com).

Results

The initial search strategy retrieved 3602 studies. Of these, two reviewers selected 564 studies for further analysis, of which 132 referred to cardiovascular drugs (fig 1). Twenty four studies fulfilled all our criteria (full details can be found at www.csmwm.org/pdf/BMJ_ethnicity_studies.pdf).

Angiotensin converting enzyme inhibitors

Angio-oedema—Six studies considered angio-oedema due to angiotensin converting enzyme (ACE) inhibitors.^{w1-w6} Pooled analysis of unadjusted data from

five studies found that black patients had a relative risk of angio-oedema of 3.0 (95% confidence interval 2.5 to 3.7) compared with non-black patients (fig 2).

Cough—Two studies presented data comparing incidence of cough due to ACE inhibitors between East Asian (Chinese, Korean, or Japanese) and white patients.^{w7 w8} The pooled relative risk calculated from the unadjusted data was 2.7 (1.6 to 4.5).

Thrombolytic therapy

Intracranial haemorrhage—The risk of intracranial haemorrhage in patients treated with thrombolytic therapy was higher in black patients than non-black patients (unadjusted pooled relative risk from two studies 1.5, 1.2 to 1.9) (fig 3).

Moderate or severe bleeding—The GUSTO-1 study reported that black patients were at increased risk of moderate or severe bleeding after treatment with thrombolytic treatment (adjusted odds ratio 1.9, 1.6 to 2.3).^{w14}

ADRs associated with other types of drug treatment

Four studies described ADRs associated with the use of antihypertensive drugs. A small clinical trial reported significantly more depression with hydrochlorothiazide in black patients than in white patients.^{w15} A prospective study, using a different measure, described a subtle difference in depression scores between black and white patients treated with antihypertensive drugs.^{w16} A small randomised controlled trial noted that the proportion of black patients reporting headache was nearly 17% compared with just over 2% in non-black patients ($P < 0.05$).^{w17} Finally, retrospective analysis of medical records by Hui and Pasic found that 26% of East Asian patients (defined as Chinese, Japanese, Filipino, Korean, and other) reported adverse effects associated with antihypertensive drugs, compared with 13% of white patients ($P < 0.002$).^{w18}

One prospective study reported non-white race (defined as black, Hispanic, or other) as a risk factor for admission to hospital because of bleeding after oral anticoagulant treatment for deep vein thrombosis (hazard ratio 1.6, 1.2 to 2.1).^{w19} Black patients were also found to have an increased risk of admission with an adverse event associated with digitalis treatment compared with white patients (odds ratio 1.37, 1.35 to 1.39).^{w20}

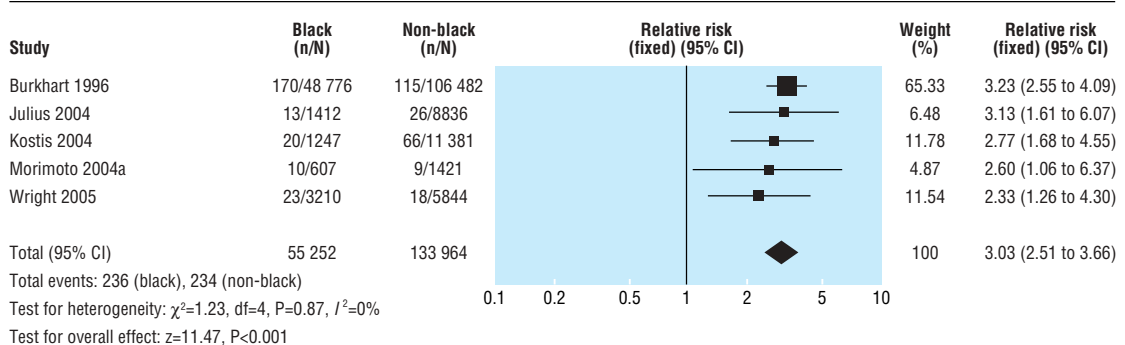


Fig 2 Pooled analysis of proportion of black and non-black patients with angio-oedema associated with use of ACE inhibitors

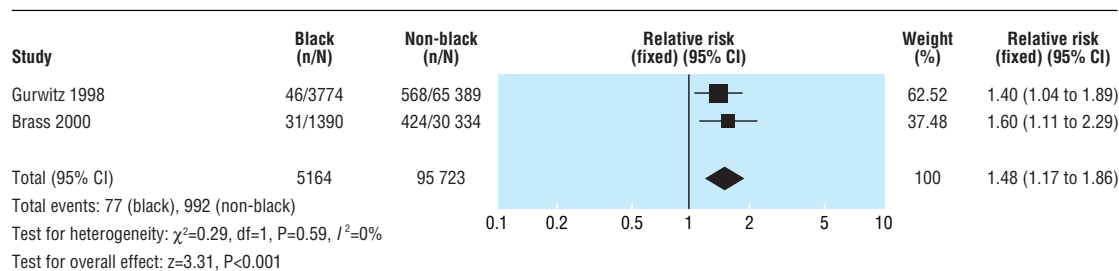


Fig 3 Pooled analysis of proportion of black and non-black patients with intracranial haemorrhage associated with thrombolytic treatment

Discussion

Our analysis supports the contention that ethnicity may predict differences in susceptibility to ADRs to cardiovascular drugs. Ethnic differences in susceptibility to ADRs of angiotensin converting enzyme inhibitors are evident and consistent with those from studies in single ethnic populations that describe a high incidence of angio-oedema in black patients,²⁰ and cough in East Asian^{21 22} and black patients.²³

Our results need to be interpreted cautiously for several reasons. The included studies differed in quality and did not report either ADRs or ethnicity consistently, which made synthesis of results between studies difficult. Data on ADRs are often not presented or are described in vague terms such as “there were no significant differences between ADRs.” Even when data on harms are reported, they are often presented for only one treatment arm or are aggregated, making it impossible to find data on specific ADRs. Studies may have been omitted from our review by the inadequate and inconsistent reporting of ADRs in the literature²⁴ or because our search strategy failed to identify relevant papers. Though we used a broad search strategy that used a combination of indexing terms and text words, literature searches may fail to identify studies that do actually report on rates of ADRs.²⁵

We excluded many studies because only data on efficacy, and not safety, were presented by ethnic group. Most studies that reported ADR data for different ethnic groups failed to describe how ethnicity was classified, thus limiting the comparison between different studies. When data were available, we sometimes combined ethnic groups to investigate the association between ethnicity and susceptibility to ADRs. This may have obscured differences within larger ethnic groups and thus limited the generalisability of the results. Consistent and transparent descriptions of assignments to well defined ethnic groups are needed.^{26 27}

Bias and confounding

The data must also be interpreted cautiously because of the risk of publication bias. Studies that reported differences in ADRs between ethnic groups may have been more likely to publish such data than studies that found no such difference or where safety analysis was not the primary focus of the project. This may have resulted in an overestimate of the risk of certain ethnic groups experiencing specific ADRs.

The included studies lacked data on possible confounding factors such as age, sex, or severity of illness by ethnic group and so we could not adjust for these. They have been shown to independently affect the risk of developing an ADR and thus may have

What is already known on this topic

Adverse drug reactions (ADRs) are an important cause of morbidity and mortality

Susceptibility to ADRs varies with genetic make up, age, sex, physiology, exogenous factors, and disease state

What this study adds

Some ethnic groups may be more susceptible to ADRs during treatment with angiotensin converting enzymes and thrombolytic drugs

Ethnic group may act as a marker for underlying genetic or environmental differences in this susceptibility

Studies investigating drug treatment need to report both adverse reactions and racial and ethnic classifications more fully

resulted in an overestimate of the true association between ethnicity and increased susceptibility to ADRs.

We did not look outside the published literature and so excluded data from unpublished drug trials and conferences. Finally, our search strategy was not designed to include studies that reported rates of ADRs in single ethnic populations because such studies necessarily rely on comparisons with other populations at different times and by different methods. This may have excluded possibly relevant information.

Conclusions

We have provided relative frequencies of ADRs in different populations that suggest the risk of harm may vary with ethnic group and may help the clinician present more accurate and relevant data to their patients when prescribing therapy. When ethnic differences in susceptibility exist, they may act as a marker for potentially important genetic or environmental factors that can influence the balance between benefit and harm and help to direct future research. This will be possible only through increased recruitment of individuals from different ethnic groups and when pharmaceutical companies report data on ethnicity routinely in the analyses of clinical trials. Furthermore, it is essential that future studies explicitly describe how the classification of ethnic group was achieved and the relevance of ethnicity to the study. This will allow for greater consistency of results and improved comparison between studies.

Our results illustrate that, for a small but well defined set of cardiovascular drugs, and a small number of ethnic groups, there is evidence that susceptibility to adverse reactions differs between ethnic groups. For a much larger group of drugs, the data do not exist to confirm or refute the existence of ethnic differences in susceptibility to ADRs.

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Effect of family style mealtimes on quality of life, physical performance, and body weight of nursing home residents: cluster randomised controlled trial

Kristel A N D Nijs, Cees de Graaf, Frans J Kok, Wija A van Staveren

Editorial by Milne, Avenell and Potter

Wageningen University, Division of Human Nutrition, PO Box 8129, 6700 EV Wageningen, Netherlands

Kristel A N D Nijs
PhD fellow

Cees de Graaf
professor

Frans J Kok
professor

Wija A van Staveren
professor emeritus

Correspondence to: K A N D Nijs
Kristel.Nijs@wur.nl

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Abstract

Objective To assess the effect of family style mealtimes on quality of life, physical performance, and body weight of nursing home residents with chronic somatic diseases.

Design Cluster randomised trial.

Setting Five Dutch nursing homes.

Participants 178 residents (mean age 77 years). Two wards in each home were randomised to intervention (95 participants) or control groups (83).

Intervention During six months the intervention group took their meals family style and the control group received the usual individual pre-plated service.

Main outcome measures Quality of life (perceived safety; autonomy; and sensory, physical, and psychosocial functioning), gross and fine motor function, and body weight.

Results The difference in change between the groups was significant for overall quality of life (6.1 units, 95%

confidence interval 2.1 to 10.3), fine motor function (1.8 units, 0.6 to 3.0), and body weight (1.5 kg, 0.6 to 2.4).

Conclusion Family style mealtimes maintain quality of life, physical performance, and body weight of nursing home residents with chronic somatic diseases.

Trial registration Clinical trials NCT00114582.

Introduction

Mealtimes in nursing homes provide an opportunity to integrate and implement physical care with measures to improve quality of life. A convivial and social environment at mealtimes might add a sense of security, meaning, order, and structure to the day and improve satisfaction with life.^{1 2}



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