Underuse of hydralazine and isosorbide dinitrate for heart failure in patients of African ancestry: a cross-European survey

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Abstract

**Aims** Population data indicate that one in 25 persons of African ancestry has heart failure, a condition with relatively high mortality of around 50% in 5 years. Combined hydralazine and isosorbide dinitrate added to conventional therapy in African ancestry patients with heart failure and reduced ejection fraction improves quality of life and reduces the rate of first hospitalization for heart failure by 33% and annual mortality by 43%. The objectives of this study were to quantify the use of this guideline-recommended therapy in Europe and the potential effect of implementation gaps on mortality.

**Methods and results** Prescription drug registration and utilization databases and population statistics were analysed in a cross-European survey without language restriction. Main outcomes were the number of unique patients prescribed the fixed combination hydralazine–isosorbide dinitrate (primary) or both drugs (secondary) in Europe in 2015, and the excess mortality related to prescribing practices was estimated. The survey indicates that around 12 million persons of African ancestry live in Europe. It is estimated that 480 000 persons of this population group have heart failure, with 120 000 eligible for hydralazine and isosorbide dinitrate therapy. However, single-pill hydralazine–isosorbide dinitrate is not authorized and therefore not dispensed in Europe in 2015. Out of the 25 European nations surveyed, the UK and the Netherlands are the only countries with major African ancestry populations where both hydralazine and isosorbide dinitrate are available for oral use, aside Norway, Sweden, and Finland. Hydralazine and isosorbide dinitrate are prescribed to <500 European patients in 2015. Thus, despite the recommendations of the European Society of Cardiology, the large majority of African-European patients with heart failure do not receive this drug combination, potentially resulting in 4800 to 5800 excess deaths yearly.

**Conclusions** The life-saving, guideline-recommended, adjunctive therapy for heart failure in African ancestry patients with hydralazine and isosorbide dinitrate is rarely used in Europe. This major evidence-practice gap should urgently be overcome to reduce excess mortality in African-European patients with heart failure.

**Keywords** Health inequities; Heart failure; African ancestry group; Mortality; Hydralazine (ATC C02DB02, PubChem CID: 3637); Isosorbide dinitrate (ATC C01DA08, PubChem CID: 6883); Hydralazine/isosorbide dinitrate combination (ATC C01DA58, PubChem CID: 9954530); Europe; Evidence-practice gap

Introduction

Heart failure (HF) is a prevalent and deadly disease among persons of African ancestry (AA). According to the American National Heart, Lung and Blood Institute, one in 25 AA persons has HF. The 5 years’ fatality rate after incident hospitalization for HF per 1000 person-years is reported to be 52% in AA men and 46% in AA women. HF in AA is of predominantly non-ischaemic aetiology, and the more severe natural history is largely explained by a greater risk factor burden of obesity,
hypertension, diabetes, and chronic kidney disease.\textsuperscript{1–7} In addition, a distinct response to pharmacotherapy is noted, with low efficacy of angiotensin-converting enzyme inhibitor therapy,\textsuperscript{4,8,9} which is thought to be associated with compromised bioavailability of nitric oxide (NO).\textsuperscript{5,9} In line with this notion, a retrospective analysis of the Vasodilator-Heart Failure Trial I indicated a significant survival benefit in AA but not European men when a combination of vasoactive drugs, hydralazine (H), an antioxidant that inhibits destruction of NO, and the NO donor isosorbide dinitrate (ISDN) was added to conventional therapy. In AA patients randomized to H + ISDN, the annual mortality ratio was 9.7% compared with 17.3% with placebo (−44%; \(P < 0.05\)), without significant difference in European patients.\textsuperscript{10} The subsequent African-American Heart Failure Trial (A-HeFT) in 1050 self-identified AA patients with New York Heart Association Class III or IV HF with dilated ventricles confirmed these findings, with a 43% reduction in mortality with fixed-dose, single-pill H–ISDN vs. placebo during a mean follow-up period of 10 months (6.2 vs. 10.2%; \(P < 0.05\)).\textsuperscript{11} In addition, a 33% relative reduction in the rate of first hospitalization for HF (16 vs. 24%; \(P < 0.05\)), a significant reduction in exacerbation of congestive HF (9 vs. 13%), and improvement in quality-of-life scores vs. placebo were reported. Headache (48 vs. 19%) and dizziness (29 vs. 12%) were the most common adverse effects reported vs. placebo.\textsuperscript{5,11,12} Although American as well as European guidelines advise H and ISDN for self-described AA patients with New York Heart Association Class III–IV HF and reduced ejection fraction,\textsuperscript{3,5,13–15} recent American studies have indicated that doctors do not prescribe this life-saving therapy to the majority of eligible hospitalized or outpatient AA patients.\textsuperscript{5} Therefore, this study analyses the implementation of this evidence in medical practice across Europe.

Outcomes

The primary outcome was the number of unique patients prescribed the fixed combination H–ISDN (as assessed in the A-HeFT). The secondary outcome was the use of both H + ISDN in unique patients as a proxy for the use of the combination. Tertiary outcomes were estimated health effects associated with prescription practices.

Methods

Design and definitions

For this survey, ‘Europe’ was defined as the European Union (EU) Member States and other European countries surveyed. To assess drug market authorization and drug use, electronic biomedical literature databases including PubMed and Embase were searched; and the European Medicines Agency (EMA) was contacted. The EMA works closely with the National Competent Authorities of the Member States of the EU and the European Economic Area responsible for human medicines. The National Competent Authorities are primarily responsible for the authorization of medicines available in the EU that do not pass through the centralized procedure.\textsuperscript{16} With a focus on European countries within the EU with relatively large African populations, European national bodies were requested for drug registration and utilization data, and demographic data of AA populations, excluding dependent territories, overseas departments, and collectivities (please view the Appendix for contact details). In line with existing literature,\textsuperscript{4,5,9–12} AA is defined as sub-Saharan African descent, either self-defined or as defined by the consulted authorities. With a non-response, at least one e-mail reminder was sent, and with a second non-response, bodies were contacted through the telephone. Data were requested of 2015 as most European bodies were able to provide these data at the time of the survey (2017 to 2018, with a pilot in December 2016). If not available, the nearest year before 2015 was requested. No language restriction was applied. Statistics are descriptive counts based on available data. The estimation of the point prevalence and mortality of HF is based on existing US evidence as explicated below. The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline was used to report the outcome data.\textsuperscript{17}

Hydralazine and isosorbide dinitrate

The European Society of Cardiology (ESC) 2012 Guidelines for treatment of HF advise combination therapy with H and ISDN for AA patients, but the drug combination is also advised with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker intolerance, to reduce the risk of hospitalization and risk of premature death in HF patients with ejection fraction ≤ 35% or ejection fraction ≤ 45% and a dilated left ventricle.\textsuperscript{14} The number needed to treat (36 months) is seven. All European cardiology societies endorse this ESC guideline,\textsuperscript{14} but there is no European performance measure for H and ISDN use. Although the guidelines mention combining H and ISDN, the FDA approved only the fixed combination H–ISDN as used in the A-HeFT.\textsuperscript{13} Real-world data indicate that mortality after 1 year of adherence is 41% higher with H + ISDN (17.0%), compared with fixed-dose H–ISDN (12.1%), a difference partly attributed to consistent simultaneous intake of both drugs and better bioavailability with the fixed combination.\textsuperscript{18}
Data or estimations on the number of persons of AA living in Europe and in Europeans nations were requested at relevant global, European, and national statistics bureaus or other relevant organizations, as for 2015, or the nearest year before 2015. If data were not available or not complete, a similar request was made at non-governmental organizations. Finally, the Internet was searched for data, mainly in online encyclopaedias. This study used the term ‘ancestry’ in contacts, but studies and other resources cited might have used ‘ethnicity’, or ‘race’, which are considered for this study to have a similar scope and meaning, referring to populations with (self-defined) sub-Saharan African heritage.

### Drug registration and utilization data

The Anatomical Therapeutic Chemical Classification (ATC) System codes for H and ISDN (Table 1) were used to search for the EU and European national data on the authorization and use of H and ISDN. The EMA and national bodies were requested whether the fixed combination H–ISDN (ATC C01DA58), H (ATC C02DB02), and (oral) ISDN (ATC C01DA08) had a market authorization for human use. Furthermore, European and national bodies were requested how many patients were prescribed the fixed combination ISDN and H or both H and ISDN in unique patients. If data on combined use in unique patient were not available, the number of patients prescribed H was used as a proxy for the maximum number of patients that could have received the combination. Data on H and ISDN use across Europe were also searched for in electronic bibliography databases including national registries, and PubMed and Embase from the inception to June 2018, using the ATC codes and the combination of key words ‘Isosorbide Dinitrate’ and ‘Hydralazine’ combined with ‘Europe’ and European country names, including the UK, England, Scotland, and (Northern) Ireland.

### Estimation of heart failure prevalence and mortality in African-Europeans

Heart failure prevalence increases with age and risk factor burden and may vary by ethnicity, sex, education level, and diagnostic criteria. In the absence of European data, the age-adjusted population prevalence in AA is estimated to be 4% based on US data. Annual HF mortality rates vary considerably across populations, with an average of 17%. Cardiac and non-cardiac factors, including sex, age, ethnicity, differences in risk factor burden, recent hospitalization for acute HF, and health care characteristics, may affect mortality. The EU (national) data on mortality of AA with HF are not available. Data from the Duke Databank of Cardiovascular Disease indicated adjusted mortality rates for HF in AA of 12% at 1 year and 49% at 5 years. In the Atherosclerosis Risk in Communities study, 76% of the prospectively followed AA population members with HF were hospitalized within 1.7 years, with an age-adjusted case fatality rate after the first hospitalization of 24% at 1 year in men and women, and 52% in men vs. 46% in women at 5 years. HF is a heterogeneous clinical entity, with a prominent distinction between patients with reduced ejection fraction (HFrEF, broadly corresponding to systolic HF) with usually a dilated left ventricular cavity size, occurring in around half of all HF patients, or preserved (HFpEF) left ventricular ejection fraction with usually a normal left ventricular cavity and concentric hypertrophy. Evidence indicates that HFpEF has a more benign prognosis than HFrEF, while H and ISDN typically improve outcomes in patients with HFrEF. After H + ISDN treatment in Vasodilator-Heart Failure Trial I (only AA men), the annual mortality rate of HFrEF was 9.7 vs. 17.3% without receiving this therapy, and in A-HeFT (AA men and women) using fixed combination H–ISDN, this was respectively 6.2 vs. 10.2%. Based on the available data, the HF population prevalence in European AA persons is estimated 4%, with 50% HFrEF, and around 25–30% of all AA HF patients to

### Table 1 Relevant ATC codes

| Level 1 | Level 2 | Level 3 | Level 4 | Level 5 |
|---------|---------|---------|---------|---------|
| Cardiovascular system | C01 Cardiac therapy | C01D Vasodilators used in cardiac diseases | C01DA Organic nitrates | C01DA08 Isosorbide dinitrate |
| | C02 Antihypertensive drugs | C02D Agents acting on arteriolar smooth muscle | C02DB Hydrazinophthalazine derivatives | C01DA58 Isosorbide dinitrate and hydralazine combinations |

Anatomical Therapeutic Chemical Classification (ATC) System codes of drugs included in this study. The ATC system is a World Health Organization Collaborating Centre for Drug Statistics Methodology used for the classification of active ingredients of drugs independent of the brand name. Each bottom-level (level 5) ATC code stands for a pharmaceutically used substance, or a combination of substances, intended for a single medical indication.19

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**Table 1 Relevant ATC codes**
benefit from H and ISDN therapy. The number of eligible patients is assumed to be at steady state, with a linear benefit of therapy over time. Annual mortality rates are conservatively estimated as 6% with and 10% without H and ISDN use, rounded to 100 persons.

Results

Despite the implementation in the ESC guidelines, H and ISDN use in the European nations surveyed appears to be negligible. Figures 1–4 and Table 2 summarize the estimated number of persons of AA and the registration and utilization of H–ISDN and its components from national drug registration and utilization databases in 25 European countries surveyed. In 2015, more than 10 years after A-HeFT was published, the collected evidence indicates that no person in Europe had received fixed H–ISDN in that year and fewer than 500 received H + ISDN.

African populations

All European and national bodies approached replied to requests for data. Except for the UK, statistics bureaus stated not to collect governmental demographics by race/ethnicity. Main data sources to estimate the number of AA persons living in continental Europe at 12 million were national statistics bureaus’ estimations based on country of birth (first and second generation migrant populations), data from the European Network Against Racism, non-governmental organizations serving the AA population, scholarly papers, and online resources (Figure 1, Table 2 and the Appendix).27–30

Market authorization, availability, and use of hydralazine and isosorbide dinitrate

No published reports were retrieved documenting the use of H and ISDN in AA patients with HF in Europe. The fixed combination H–ISDN was not authorized at the EMA or within any European nation (Figure 2). In addition, in many countries including France, commercially prepared oral H or oral ISDN
was unavailable (Figure 3 and Table 2). In general, magistral preparations were not nationally registered, but some countries, such as Norway and Sweden, did file every prescription, while others, such as Denmark and Belgium, filed medicine sales. Both Denmark and Belgium indicated that pharmacies’ production volumes for individual patients would by EU law be very low.31

The total number of persons using the fixed combination H–ISDN in Europe was nil (Table 2). As neither H nor ISDN has a centralized (EU) market authorization, the combined use in countries was considered to be nil if oral H or oral ISDN did not have a national market authorization or were unavailable, but confirmation was requested at national bodies that register drug use. Poland and Latvia did not have data to confirm that no unique patient used both H and ISDN, but there was no market authorization for H in either country.

Of the five countries where both oral H and oral ISDN were available (Figure 3 and Table 2), data from Norway and Sweden include all pharmaceutical drug sales (for Norway including hospital data), from Finland contain all reimbursed prescription drugs, while the UK and the Netherlands provided data on reimbursed drugs to outpatients only. With the focus on chronic care, >100 000 unique patients using these drugs were expected (Table 2). However, combined use of commercially available (pharmaceutical) H and ISDN in unique, non-hospitalized patients across Europe was negligible at <500 in 2015 (Figure 4). Only Belgium reported the use of magistral preparations of H, in <250 patients in 2015. Thus, less than 1% of European AA patients with HF could have received any combination of H and ISDN for chronic HF care (Table 2). At the expense of potential side effects, mainly headache and dizziness, the use of this drug combination might have substantially reduced premature mortality with 4800 to 5800 AA HF patients yearly.

**Discussion**

This study provides evidence of a significant care gap in best practice of HF treatment provided to persons of AA across Europe. Although there is evidence from randomized controlled trials and real-world studies on the reduction of HF
Table 2  The use of hydralazine (H) and isosorbide dinitrate (ISDN) combination therapy in Europe

| Region                  | Data source | African ancestry (n) | Eligible HF patients | African ancestry populationa | Marketing authorizationc | H and ISDN useg |
|-------------------------|-------------|----------------------|----------------------|-----------------------------|-------------------------|---------------|
| European Union          | UN; ENAR    | 9 000 000–15 000 000 | 144 000              | EMA n.a. n.a. n.a. Eurostat | EU n.d.                |
| France                  | ENAR; Insee; Cran | 2 000 000–5 000 000 | 42 000               | ANSM n.a. n.a. + Ameli       | National 0             |
| UK                      | ONS         | 2 200 000–2 900 000 | 30 600               | MHRa n.a. + + THIN 20% NP   | 35h National 0         |
| Spain                   | ENAR; INE   | 800 000–1 000 000   | 10 800               | AEMPS CIMA n.a. + +         | Ministério de Sanidade National 0 |
| Germany                 | ENAR; UNAR; ISD | 800 000–1 000 000  | 10 800               | Pharmnet BfArM n.a. n.a.   | DAPI 90% NP 0          |
| The Netherlands         | ENAR; CBS   | 750 000–900 000     | 10 500               | CBG n.a. + + GIP/ZIN        | National 64h           |
| Belgium                 | Wikipedia; Statbel; MECM | 500 000      | 6000                 | FAGG n.a. n.a. +           | Farmanet/RIZIV National 0 |
| Italy                   | ENAR; ISTAT | 500 000              | 6000                 | AIFA n.a. n.a. +           | National 0             |
| Portugal                | Afropedia INE; SEF | 300 000–500 000     | 4800                 | Infarmed n.a. n.a. +       | National 0             |
| Norway                  | SSB         | 210 000              | 2500                 | NoMA n.a. + + NorPD         | National 24h           |
| Sweden                  | SCB; ASR; MKC | 200 000              | 2400                 | MPA n.a. + + Social-styrelsen | National 4h           |
| Ireland                 | ENAR; Cso   | 70 000               | 800                  | HPRA n.a. + + HSE-PCRS      | National 0             |
| Denmark                 | DST; AEC    | 65 000               | 800                  | DHA n.a. n.a. +            | MEDSTAT National 0     |
| Austria                 | Wikipedia; SA; Sauer27b | 40 000     | 500                  | BASG AGES n.a. n.a. Haupt-verband EKO | National 0 |
| Finland                 | EAES; SF   | 30 000               | 400                  | Fimea n.a. + + KELA         | National 0n            |
| Poland                  | SP; Zabek28 | <10 000              | <100                 | URPL SCIOZd n.a. n.a. +    | NFZ National 0         |
| Bulgaria                | EAES; NSI  | <10 000              | <100                 | BDA n.a. n.a. + BDA         | National 0             |
| Hungary                 | KSHh       | <10 000              | <100                 | OGYEI n.a. n.a. o.         | OGYEI National 0       |
| Croatia                 | DZS        | <10 000              | <100                 | HALMED n.a. n.a. –         | HALMED National 0      |
| Czech Republic          | CZSO       | <10 000              | <100                 | Suki n.a. n.a. + Suki      | National 0             |
| Iceland                 | EAES; Statice | <1000              | <10                  | IMA n.a. n.a. + Embæt Epidemiologi ländskab   | National 0 |
| Estonia                 | SEy        | <1000                | <10                  | SAM n.a. n.a. + SAM        | National 0             |
| Latvia                  | CSB        | <1000                | <10                  | ZVA n.a. n.a. + ZVA         | National 0             |
| Lithuania               | SL         | <1000                | <10                  | VVK n.a. n.a. + VKL         | National 0             |
| Slovakia                | SOSR       | <1000                | <10                  | SUKL n.a. n.a. + SUKL       | National 0             |
| Montenegro              | Wikipedia; MONSTAT | <1000           | <10                  | CALIMS n.a. n.a. + CALIMS   | National 0             |

Data are from 2015 (or nearest preceding year). A list of abbreviations and organizations’ contact details is provided in the Appendix.

aData are estimates on the number of African ancestry (AA) persons living in the European Union (EU) and European nations (excluding dependencies).

bHungary and Estonia population data were from 2011 and Austria from 2005. The midpoint value of a range was used to estimate the number of persons with heart failure (HF), detailed in the Method section. Numbers were rounded to the nearest 100 (or 10 for <100).

cCentralized (EU) and national data on market authorization of oral preparations of the fixed drug combination hydralazine and isosorbide dinitrate, H–ISDN, or its components. Plus sign (+), authorized drug; n.a, not authorized.

dAuthorization data from Poland include centralized (EU) and parallel import authorization.

Only 5 mg sublingual ISDN available.

Number of unique persons, receiving both H and ISDN as pharmaceutical (prescription) drugs at least once in 2015; zero includes no market authorization for hydralazine and/or isosorbide dinitrate. Most registries provide data of reimbursed pharmaceutical H and ISDN, prescribed to non-hospitalized patients.

The UK and the Netherlands report reimbursed drugs to outpatients, Norway and Sweden include all pharmaceutical drug sales (Norway including hospital data), and Finland reports all reimbursed prescription drugs. NP, national population; n.d. no data.
mortality in AA patients with H and ISDN adjunctive therapy,10–15,18,25 the fixed combination is not authorized in the EU or in the European nations surveyed, and the availability of both components H and ISDN is very limited, to five countries. In the absence of a European performance measure for clinical practice, the use of this guideline-recommended therapy14,32 is negligible at less than 500 unique patients throughout Europe in 2015.

Because of this major discrepancy between best practice and care provided in usual clinical practice, 4800 to 5800 of African-European HF patients may die prematurely each year. This estimation is conservatively based on a 40% reduction in mortality with H–ISDN from 10 to 6%, while real-world data indicate that annual mortality rates in AA HF patients might be considerably higher,18,21,22,26 in particular when the fixed combination is not used.18 These findings should have significant clinical and public health policy implications, to ensure that the ESC guideline-recommended therapy with H and ISDN32 is applied and optimal care is provided to AA HF patients.

Strengths and limitations of this study

The study is to our knowledge the first to report the performance of European health care regarding H and ISDN, with negligible use as the main outcome. Although this study represents the best estimate of drug use, it required the gathering of data from heterogeneous sources that might have utilized different definitions and criteria for H and ISDN use and for being of ‘sub-Saharan African ancestry’. Furthermore, there is a lack of data on drug dose and on prescription patterns in time or by age and sex, while data from European countries with very small AA populations were not exhaustively collected in this study. Also, many national bodies provided data on reimbursed drugs only. However, European countries have a universal health care system that provides health care and financial protection to >90% of the citizens.33 Because H is poorly available, it is highly unlikely that further data would change the magnitude of the main study outcome of negligible H and ISDN use in Europe. Regarding the tertiary outcome of health effects associated with this limited use, the assumptions might have underestimated or overestimated true effects in African-European populations, as the estimation of HF epidemiology, effectiveness of H and ISDN, and the outcomes are based on US data. Significant East AA populations live in Europe, and there are no data whether the specific benefit of H and ISDN established in predominantly West African population is similar in these groups. Finally, because of the explorative nature of this study, only the impacts on reduction in deaths are estimated, not on hospitalizations, improvement in quality of life, cost-effectiveness, or other important clinical or health economic outcomes.

Implications for policy and practice

Lack of availability of hydralazine–isosorbide dinitrate and its components in Europe

Both H and ISDN are on WHO Model List of Essential Medicines.34 The list includes H (25/50 mg) for hypertension during pregnancy and sublingual ISDN (5 mg) for angina pectoris but not oral ISDN. Pharmaceuticals with a priority health care need are intended to be available within the context of functioning health systems with stable and reliable stocks, in the appropriate dosage forms and with assured quality.34 However, H was not available in most EU countries. The question why drugs are not marketed or available was beyond the scope of this study, but with a free market, profitability is probably a factor.

Shortage of pharmaceuticals is an increasing problem within Europe. The health status of patients is put at risk if they are not receiving their prescribed medicines in a timely manner. The Heads of Medicines Agencies (HMA) is a network of the heads of the National Competent Authorities, whose organizations are responsible for the regulation of medicinal products in the European Economic Area. While throughout Europe there is no harmonized definition of ‘drug shortages’, the HMA has identified what types of drug shortages are most critical, and the definition includes pharmaceutical for which there is a medical need but that are not authorized or not marketed in a Member State.35 However, nor the joint Task Force on Availability of Authorised Medicines for human and veterinary use, created by the HMA and the EMA and dedicated to the availability of authorized medicinal products for human use, nor its different Network Members consider H–ISDN fixed combination or its components in their evaluation of shortages.35 This renders it nearly impossible for health workers in the majority of European nations to prescribe the fixed drug combination or its components other than magistral preparations, which are by law not intended for widespread use.31 Moreover, the use of the components of H–ISDN for HF might in some health systems be considered off-label use.18 Thus, the use of the combination therapy should be properly registered, and the fixed combination H–ISDN and/or its components should become available across Europe for use for HF in AA patients.

Definition and statistical invisibility of African ancestry populations in Europe

A main issue regarding the evaluation of the use of H–ISDN is the ‘statistical invisibility’ of AA populations across Europe. Broadly, persons of sub-Saharan African or their ancestors migrated to Western European countries from continental Africa or from the Americas. Refugees from Africa form a special category, having a marked impact on the size of African population in countries without long-established African communities, such as Ireland, Switzerland, and the Nordic countries.36 Hence, Europe’s African population is very
diverse with members of established AA communities, such as in England, France, and the Netherlands, as well as recent migrants. However, except for the UK and Ireland, no national or European statistical or health data are collected on this population subgroup. As a consequence, despite (self-)identification in the doctor–patient relationship, statistically speaking, AA persons in mainland Europe do not exist. This statistical ‘colour blindness’—meant to protect individuals—may impede the health of African populations. The EU Agency for Fundamental Rights has concluded that Africans ancestry populations belong to the most vulnerable groups in the EU. African populations may require special health care, such as screening for cardiovascular disease, adjusted guidelines, and performance measures. On the other hand, many scholars argue that ‘Blackness’ is a sociologically constructed identity that has historically been imposed on people. This matter is circumvented through self-identification of AA, but a biomarker to identify individuals who might benefit from H and ISDN therapy would be helpful. H has an antioxidant effect that enhances and sustains the efficacy of nitrates. This suggests that patients with compromised NO generation might benefit from the therapy. Relatively low L-arginine, associated with high creatine kinase activity and creatine synthesis, and glucose-6-phosphate dehydrogenase deficiency have been suggested to induce low NO bioavailability, and assessments of these enzyme systems might help predict responses to H and ISDN. Also, G-protein beta-3 subunit genotype was reported to predict the response to H and ISDN, but to date, no biomarker has been validated for clinical use, and self-identified AA remains the best available predictor for benefit from H and ISDN therapy. The lack of consensus on categories based on ancestry and inconsistent data collection are major hindrances for European health outcome assessments by AA. This difficulty in assessing data extends the problem of a significant evidence-practice gap in the care of AA patients with HF.

Conclusions

This survey provides preliminary evidence that patients of AA in Europe with HF might experience excess mortality because of an unmet therapeutic need, as the guideline-recommended, life-saving adjunctive combination therapy with H and ISDN is not available or not prescribed. Aside primary prevention of HF—in particular the early detection and adequate treatment of hypertension—access to and use of this life-prolonging therapy with H and ISDN are imperative to reduce premature mortality in AA patients with HF.

Conflict of interest

None declared.

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Author contributors

L.M.B. designed the study, collected, and analysed the data, drafted and revised the manuscript, and is the guarantor of the study. The corresponding author attests that no others meeting the criteria have been omitted.

Appendix

Contact information of the organizations surveyed

| Location | Namea | Acronym | URL |
|----------|-------|---------|-----|
| EU       | European Medicines Agency | EMA | http://www.ema.europa.eu |
|          | Eurostat | n.a. | http://ec.europa.eu/eurostat |
| France   | Agence Nationale de Sécurité du Médicament et des Produits de Santé, (National Agency for the Safety of Medicine and Health Products) Assurance Maladie pour les médecins (French Health Insurance) | ANSM | http://ansm.sante.fr |
|          | | | http://agence-prd.anms.sante.fr |
|          | | ameli | https://www.ameli.fr |
| UK       | Medicines and Healthcare Products Regulatory Agency | MHRA | http://www.mhra.gov.uk |

(Continues)
| Location | Namea | Acronym | URL |
|----------|--------|---------|-----|
| Spain | Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Health Products) | AEMPS | https://www.aemps.gob.es |
| Spain | Centro de Información Online de Medicamentos de la AEMPS Medicine (Online Information Center of AEMPS) | CIMA | https://www.aemps.gob.es/cima |
| Germany | Pharmnet.Bund | n.a. | https://www.msssi.gob.es |
| Germany | Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices) | BfArM | https://www.bfarm.de |
| Germany | Deutsches Arzneimittelverwertungsinstitut e.V. (German Institute for Drug Use Evaluation) | DAPI | http://www.dapi.de |
| The Netherlands | College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board) | CBG | https://www.cbg-meb.nl |
| The Netherlands | Genees- en hulpmiddelen Informatie Project (The Drug Information System of National Health Care Institute) | GIP/ZIN | https://www.geneesmiddelen-informatiebank.nl |
| Belgium | Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG) or Agence Fédérale des Médicaments et des Produits de Santé (AFMPS). (The Federal Agency for Medicines and Health Products; FAMHP) | FAGG | https://www.fagg-afmps.be |
| Belgium | Farmarinet database, Rijksinstituut voor ziekte- en invaliditeitsverzekering | Farmanet RIZIV | https://www.riziv.fgov.be |
| Italy | Agenzia Italiana del Farmaco (Italian Medicines Agency) | AIFA | http://www.aifa.gov.it |
| Portugal | Autoridade Nacional do Medicamento e Produtos de Saúde (National Authority for Medicines and Health Products) | Infarmed | http://www.infarmed.pt |
| Norway | Statens legemiddelverk (The Norwegian Medicines Agency) | NoMA | https://legemiddelverket.no |
| Norway | Norwegian Prescription Database | NorPD | http://www.norpd.no |
| Sweden | Läkemedelsverket (Swedish Medical Products Agency) | MPA | https://lakemedelsverket.se |
| Sweden | Socialstyrelsen (The National Board of Health and Welfare) | n.a. | https://www.socialstyrelsen.se |
| Ireland | Health Products Regulatory Authority | HPRA | https://www.hpra.ie |
| Ireland | Health Service Executive–Primary Care Reimbursement Service | HSE-PCRS | https://www.hse.ie |
| Denmark | Laegemiddelstyrelsen (Danish Medicines Agency) | DMA | https://laegemiddelstyrelsen.dk |
| Denmark | The Danish Health Data Authority Health Analysis, Medicinal Product Statistics & Health Data Program | MEDSTAT | https://medstat.dk |
| Austria | Bundesausschuss für Sicherheit im Gesundheitswesen (Austrian Federal Office for Safety in Health Care) | BASG | https://www.basg.gv.at |
| Austria | Österreichischen Agentur für Gesundheit und Ernährungssicherheit (Austrian Medicines and Medical Devices Agency), Arzneispezialitätenregister/PharmaIS Web | AGES | https://aspreregister.basg.gv.at |
| Austria | Der Hauptverband der Österreichischen Sozialversicherungsträger (The main association of Austrian social security institutions) | Hauptverband | http://www.hauptverband.at |
| Austria | Erstattungskodex (Reimbursement Codex) | Eko | https://www.sozialversicherung.at/eko |
| Austria | | | http://oertl.at/eko |
| Finland | Finnish Medicines Agency | Fimea | http://www.fimea.fi |
| Poland | Urząd Rejestracji Produktów Leczniczych, Wyrobów Medycznych i Produktów Biobójczych (URPLWMPbP) (Office for Registration of Medicinal Products, Medical Devices and Biocidal Products) | KELA | http://www.kela.fi |
| Poland | Rejestrzy medyczne, Centrum Systemów Informacyjnych Ochrony Zdrowia (Center for Health Information Systems) | URPL | http://urpl.gov.pl |
| Bulgaria | The Bulgarian Drug Agency | NFZ | http://www.nfz.gov.pl/ |
| Hungary | Országos Gyógyszerészeti és Élelmézés-egészségügyi Intézet (National Institute of Pharmacy and Nutrition) | OGYEI | https://www.ogyei.gov.hu |

(Continues)
### Table A1 (continued)

| Location          | Name\(^a\)                                                                 | Acronym | URL                                           |
|-------------------|---------------------------------------------------------------------------|---------|------------------------------------------------|
| Croatia           | Hrvatska agencija za lijekove i medicinske proizvode (Croatian Agency for Medicinal Products and Medical Devices) | HALMED  | http://www.halmed.hr                           |
| Czech Republic    | Státní ústav pro kontrolu léčiv (State Institute for Drug Control)       | SÚKL    | http://www.sukl.cz                             |
| Iceland           | The Icelandic Medicines Agency                                            | IMA     | https://www.imais.is                            |
| Estonia           | Ravimiamet (State Agency of Medicines)                                    | n.a.    | https://www.landiaknis.is                      |
| Latvia            | Zāļu valsts a entūra (State Agency of Medicines of the Republic of Latvia) | ZVA     | https://www.zva.gov.lv                         |
| Lithuania         | Valstybinė vaistų kontrolės tarnyba (State Medicines Control Agency)       | VVKT    | http://www.vvtk.lt/                            |
| Slovakia          | Státny ústav pre kontrolu liečiv (State Institute for Drug Control)       | ŠÚKL    | https://www.sukl.sk                            |
| Montenegro        | Crne Gore Agencija za lijekove i medicinska sredstva (Agency for Medicines and Medical Devices of Montenegro) | CALIMS  | https://www.calims.me                          |

Contact information of the organizations surveyed.

\(^a\)Official English nomenclature where applicable and available in round brackets. EU, European Union; n.a., not applicable; URL, uniform resource locator, valid as for 18 November 2018.

### Table A2 African ancestry population data

| Location  | Name\(^a\)                                                                 | Acronym | URL                                           |
|-----------|---------------------------------------------------------------------------|---------|------------------------------------------------|
| Global    | United Nations                                                            | UN      | https://www.un.org                            |
| EU        | The European Network Against Racism                                       | ENAR    | https://www.enar-eu.org                       |
| WWW       | Encyclopedia of Afro-European Studies                                     | EAES    | http://www.encyclopediaofaforeuropeanstudies.eu |
|           | Afropedia                                                                  | n.a.    | http://www.afropedea.org                      |
|           | Wikipedia                                                                  | n.a.    | http://www.wikipedia.org                      |
| France    | Institut national de la statistique et des études économiques (National Institute of Statistics and Economic Studies) | Insee   | https://www.insee.fr                          |
|           | Le Conseil représentatif des associations noires de France                | CRAN    | https://le-cran.fr                            |
| UK        | Office for National Statistics                                            | ONS     | https://www.ons.gov.uk                        |
| Spain     | Instituto Nacional de Estadistica (National Statistics Institute)         | INE     | http://www.ine.es                             |
| Germany   | Statistisches Bundesamt (Initiative Schwarze Menschen in Deutschland (Initiative Black People in Germany) | Destatis | https://www.destatis.de                        |
|           | Initiative of Statistics                                                  | ISD     | http://isdonline.de                           |
| The Netherlands | Centraal Bureau voor de Statistiek (Statistics Netherlands)     | CBS     | https://www.cbs.nl                            |
| Belgium   | Algemene Directie Statistiek (Statistics Belgium)                         | Statbel | https://statbel.fgov.be                       |
|           | Forum van Etnisch-Culturele Minderheden, (Minority Forum)                | MECM    | http://www.minderhedenforum.be                |
| Italy     | Istituto Nazionale di Statistica (National Institute of Statistics)      | ISTAT   | https://www.istat.it                           |
| Portugal  | Instituto Nacional de Estatistica (Statistics Portugal)                  | INE     | https://www.ine.pt                            |
|           | Serviço de Estrangeiros e Fronteiras, Portal de Estatistica. (Portuguese Immigration and Border Service, Statistics Portal) | SEF     | http://sefstat.sef.pt                          |
| Norway    | Statistisk sentralbyrå (Statistics Norway)                                | SSB     | https://www.ssb.no                             |
| Sweden    | Statistiska centralbyrå (Statistics Sweden)                               | SCB     | http://www.scb.se                             |
|           | Afrosvenskarnas riksfölbund (The Afro-Swedish National Association)       | ASR     | http://www.afrosvenskarna.se                  |
|           | Mångkulturellt centrum (The Multicultural centre)                        | MKC     | http://mkcentrum.se                           |
| Ireland   | Central Statistics Office Ireland                                        | CSO     | https://www.cso.ie                            |
| Danmark   | Danmarks Statistik (Statistics Denmark)                                    | DST     | https://www.dst.dk                            |
|           | Afro Empowerment Center Denmark                                           | AEC     | http://www.aec-cph.dk                         |

(Continues)
Table A1 (continued)

| Location          | Namea                                      | Acronym | URL                           |
|-------------------|--------------------------------------------|---------|-------------------------------|
| Austria           | Bundesanstalt Statistik Österreich (Statistics Austria) | SA       | http://www.statistik.at       |
| Finland           | Statistics Finland                          | SF      | https://www.stat.fi           |
| Poland            | Główny Urzad Statystyczny (Statistics Poland) | SP      | https://stat.gov.pl           |
| Bulgaria          | National Statistical Institute             | NSI     | http://www.nsi.bg             |
| Hungary           | Kossptsi Statisztikai Hivatal (Hungarian Central Statistical Office) | KSH     | https://www.ksh.hu            |
| Croatia           | Državni zavod za statistiku (Croatian Bureau of Statistics) | DZS     | https://www.dzs.hr            |
| Czech Republic    | Český statisticky úřad/Czech Statistical Office | CZSO    | https://www.czso.cz           |
| Iceland           | Hangstað Islands (Statistics Iceland)      | Statice | http://statice.is             |
| Estonia           | Statistikaamet (Statistics Estonia)        | SE      | http://pub.stat.ee            |
| Latvia            | Latvijas statistika (Central Statistical CSB  | http://www.csb.gov.lv         |
| Lithuania         | Statistics Lithuania                       | SL      | https://www.stat.gov.lt/en    |
| Slovakia          | Statistical Office of the Slovak Republic  | SOSR    | https://slovak.statistics.sk   |
| Montenegro        | Zavod za statistiku Crne Gore (Statistical Office of Montenegro) | MONSTAT | http://www.monstat.org        |

aContact information of the organizations surveyed.
bOfficial English nomenclature where applicable and available in round brackets. EU, European Union; WWW, World Wide Web; n.a., not applicable; URL, uniform resource locator, valid as for 18 November 2018.

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