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Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis

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Aims The effect of resistant hypertension on outcomes in patients with atherothrombotic disease is currently unknown. Accordingly, we sought to determine the prevalence and outcomes of resistant hypertension in stable hypertensive outpatients with subclinical or established atherothombotic disease enrolled in the international Reduction of Atherothrombosis for Continued Health (REACH) registry.

Methods and results Resistant hypertension was defined as a blood pressure ≥140/90 mmHg at baseline (≥130/80 mmHg if diabetes/renal insufficiency) with the use of ≥3 antihypertensive medications, including a diuretic. The primary outcome was a composite of cardiovascular death, myocardial infarction, or stroke at 4 years. A total of 53 530 hypertensive patients were included. The prevalence of resistant hypertension was 12.7%; 6.2% on 3 antihypertensive agents, 4.6% on 4 agents, and 1.9% on ≥5 agents (mean: 4.7 ± 0.8). In addition to a diuretic, these patients were being treated mostly with ACE-inhibitors/angiotensin receptor blockers (90.1%), beta-blockers (67.0%), and calcium channel blockers (50.8%). Patients with resistant hypertension had a higher risk of the primary endpoint on multivariable analysis [hazard ratio (HR) 1.11, 95% confidence interval (CI) 1.02–1.20; $P = 0.017$], including an increased non-fatal stroke risk (HR: 1.26; 95% CI: 1.10–1.45; $P = 0.0008$). Hospitalizations due to congestive heart failure were higher ($P < 0.0001$). Patients on ≥5 agents had a higher adjusted risk for the primary endpoint when compared with those on ≤3 agents ($P = 0.03$).

Conclusion The presence of resistant hypertension identifies a subgroup of patients with hypertension and atherothrombosis who are at heightened risk for adverse long-term outcomes.

Keywords Resistant hypertension • Atherosclerosis • Mortality • Stroke • Heart failure

Introduction

Hypertension is a major public health problem globally, with 28% of adults in North America and 44% in Europe being hypertensive.[1,2] It is also one of the most important modifiable risk factors for cardiovascular morbidity and mortality, especially for stroke (accounting for 51% of all stroke deaths worldwide), ischaemic heart disease (45% of all deaths), chronic kidney disease (CKD), congestive heart failure, aortic aneurysms, and peripheral arterial disease.[3,4] Patients with resistant hypertension represent

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a higher risk subset of patients with hypertension. The USA Joint National Committee (JNC)-7 defines resistant hypertension as failure to achieve goal blood pressure (BP) (<140/90 mmHg for the overall population and <130/80 mmHg for those with diabetes mellitus or CKD) despite adhering to maximum tolerated doses of three antihypertensive drugs including a diuretic.[5] A similar definition has been adopted by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC).[6]

Despite a standardized definition, the true incidence and prevalence of resistant hypertension in the general population is difficult to estimate. Prevalence estimates indicate that 3–33% of patients with hypertension may have resistant hypertension, and a recent study indicated that the incidence of resistant hypertension was 0.7 cases per 100 person-years among patients with new-onset hypertension.[7–12] Atherothrombosis [coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD)] is another ubiquitous cause of mortality and morbidity. There is a significant overlap between patients with hypertension and atherothrombosis—nearly 40% of patients with established CAD and 53% with acute myocardial infarction in the INTERHEART study had evidence of hypertension.[13] However, hypertension is frequently not well controlled in these patients.[14] The exact prevalence of resistant hypertension in patients with atherothrombosis is unknown currently, and when co-existent, the combination is likely to be associated with significant deleterious consequences.

The Reduction of Atherothrombosis for Continued Health (REACH) Registry is one of the largest contemporary outpatient registries that was initiated to evaluate patients who would represent the entire spectrum of stable atherosclerotic clinical syndromes: from those with risk factors (but who are asymptomatic) to those with established atherosclerotic arterial disease within any circulatory bed. Being an international registry, it has the additional advantage of being representative of geographically and ethnically diverse populations.[15] We sought to study the prevalence of resistant hypertension in patients enrolled in this registry, and their long-term clinical outcomes.

Methods

Data source

The methods of the REACH Registry have been published in detail before.[16–19] This protocol was submitted to institutional review boards in each country according to the local requirements and signed informed consent was required for all patients. In brief, patients at least 45 years old with three or more risk factors for atherosclerosis, and patients with established CAD, CVD, or PAD were enrolled. Qualifying risk factors were diabetes, diabetic nephropathy, ankle-brachial index <0.9, asymptomatic carotid stenosis of 70% or more, carotid intima media thickness at least two times that at adjacent sites, systolic BP of ≥150 mmHg despite treatment, hypercholesterolaemia treated with medication, current smoking of 15 or more cigarettes per day, and age ≥65 years for males or ≥70 years for females. Race/ethnicity was self-reported. Established CAD consisted of ≥1 of the following: stable angina, history of unstable angina, history of percutaneous coronary intervention, history of coronary artery bypass grafting, or previous MI. Established CVD consisted of a neurologist report or hospital report with the diagnosis of ischaemic stroke or transient ischaemic attack. Established PAD consisted of current intermittent claudication with the ankle-brachial index of l<0.9 and/or a history of intermittent claudication together with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass grafting, or other vascular interventions, including amputations.

Selection of physicians to the REACH Registry was determined at the country level. To ensure homogeneity and a good representation in the REACH Registry population, a site selection method was designed and implemented in each participating country by epidemiologists under the supervision of the REACH Registry global and local steering committees and national coordinators. This selection was designed to try to mimic the best available epidemiological data in each country that reflect the burden of atherothrombosis or at-risk populations.[15]

Study population

At the time of final database lock in April 2009, 69 055 patients from 5587 physician practices in 44 countries between December 2003 and June 2004, and followed up until 2008, had been enrolled. From this, we excluded 1167 patients without baseline information, and 2710 patients without adequate follow-up. Of the 65 526 patients eligible for analysis, we further excluded 11 996 patients with no reported history of hypertension (*Figure 1*).

Follow-up

Following enrolment (baseline), patients underwent annual follow-up at 1, 2, 3, and 4 years. Although the study was initially planned for 2 years, an additional 2-year extension was proposed shortly before that period ended. Not all countries and sites that were in the 2-year follow-up cohort elected to continue participation in the registry, although the majority did elect to continue ($n = 36\,752$). Patients without 4-year follow-up were censored at the time of the last visit, unless they had already experienced an event.

Ascertainment of exposure

Blood pressure was measured at the time of enrolment in a seated position after at least 5 min of rest. Patients with hypertension were defined as those who were previously or currently being treated with antihypertensive agent(s). Medications were grouped based on drug class [angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers, diuretics, nitrates, other agents]. Dose was not recorded. Resistant hypertension was defined as a BP ≥140/90 mmHg (≥130/80 mmHg if diabetes mellitus or CKD) at the time of enrolment into the REACH registry, with the concomitant use of ≥3 antihypertensive medications, including a diuretic.[5]

Ascertainment of outcomes

The primary outcome was a composite of cardiovascular death, myocardial infarction, or stroke over 4 years. Other endpoints included all-cause and cardiovascular mortality, all strokes, non-fatal myocardial infarction, cardiovascular hospitalizations, and hospitalization due to congestive heart failure. Endpoints were not adjudicated, but based on physician reporting at the time of follow-up. Cardiovascular death included fatal stroke, fatal myocardial infarction, or other cardiovascular death. Other cardiovascular death included other death of cardiac origin; pulmonary embolism; any sudden death including unobserved and unexpected death (e.g. death while sleeping) unless proven otherwise by autopsy; death following a vascular operation, vascular

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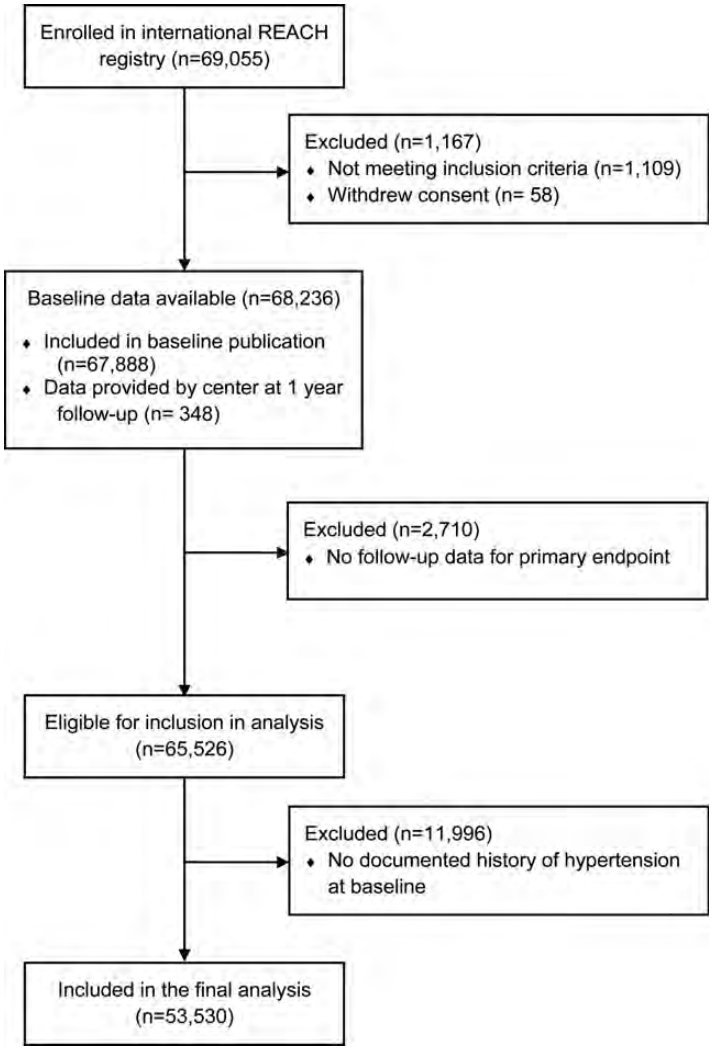

Figure 1 CONSORT flow diagram of study participants.

procedure, or amputation; death attributed to congestive heart failure; death following a visceral or limb infarction; and any other death that could not be definitely attributed to a non-vascular cause or haemorrhage. Any myocardial infarction or stroke followed by a death whatever the cause in the next 28 days was considered to be a fatal myocardial infarction or fatal stroke. Cardiovascular hospitalization consisted of hospitalization for unstable angina, transient ischaemic attack, worsening of claudication related to PAD, other ischaemic arterial event, coronary artery bypass grafting, coronary angioplasty/stenting, carotid surgery, carotid angioplasty/stenting, amputation affecting lower limbs, peripheral bypass graft, or angioplasty/stenting for PAD.

Statistical analysis

Mean ($\pm$standard deviation) and percentages are reported for continuous and categorical variables, respectively. Cumulative incidence rates and curves were constructed using the Kaplan–Meier approach. Multivariable Cox regression analyses were conducted, with time to cardiovascular death, myocardial infarction or stroke as the primary outcome variable, and resistant hypertension as the primary independent variable. Multivariate Cox models were similarly constructed for all other outcomes, with the exception of cardiovascular hospitalization and hospitalization for congestive heart failure, for which multivariate logistic regression models were constructed. The absence of information on exact date of hospitalization precluded time to event analyses for these two models. Hazard ratios (HR) or odds ratios (OR) and their 95% confidence intervals (CI) were calculated. Other variables included in these models have all been shown to be significant independent predictors of the primary outcome at 4 years in a prior analysis.[17] These include: gender, age, current smoker, history of diabetes, body mass index <20 (calculated as weight in kilograms divided by height in meters squared), timing of ischaemic event (no event, ≤ 1 year, >1 year), risk factors only vs. established disease, polyvascular disease vs. single-bed disease, baseline use of aspirin and statins, congestive heart failure, atrial fibrillation/flutter, and Eastern Europe and Middle East vs. Japan, and Australia vs. other regions. Given the importance of renal function in determining outcomes in patients with hypertension,[20] the presence of CKD was additionally included in the final multivariate model.

A number of additional analyses were conducted. Although nitrates can be utilized for hypertension management, they are not included in

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the JNC-7 definition of oral antihypertensive agents. Accordingly, we repeated the primary analysis by excluding nitrates from the definition of resistant hypertension. We also analysed outcomes based on number of antihypertensive medications utilized (<3, 3, 4, or ≥5) in these patients. As a form of sensitivity analysis, we repeated the primary analysis with conservative and liberal definitions of resistant hypertension. For the conservative definition, only patients with baseline systolic BP ≥160 mmHg were defined as having resistant hypertension. For the liberal definition, resistant hypertension was defined as uncontrolled BP (≥140/90 mmHg, or ≥130/80 mmHg if diabetes or CKD) on 3 agents, or the concomitant use of ≥4 antihypertensive medications (including a diuretic), irrespective of BP. Thus, patients who were on 4 or more antihypertensive agents, but had controlled BPs, were included in the analysis.

The proportional hazards assumption for the hypertension status (resistant vs. non-resistant) was tested for all models included in the analysis. Where a violation was present, the Cox model was adapted to include an adjustment for the log transformation of follow-up time; HRs are reported at a median follow-up time for these endpoints. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). All *P* values were two-tailed, with statistical significance set at 0.05. All CIs were calculated at the 95% level.

Results

A total of 53 530 patients were included, of whom 6790 patients (12.7%) met our definition of resistant hypertension. Of these, 6.2% were on 3 antihypertensive agents, 4.6% on 4 agents, and 1.9% of ≥5 agents (mean: 4.7 ± 0.8). Agents used included ACE-inhibitors (63.3%), angiotensin receptor blockers (33.1%), ACE-inhibitors or angiotensin receptor blockers (90.1%), beta-blockers (67.0%), calcium channel blockers (50.8%), nitrates (35.6%), and other miscellaneous agents (19.0%); by definition all patients were on a diuretic (*Figure 2*). Baseline characteristics of the study population are presented in *Table 1*. Patients with resistant hypertension were more likely to be younger, female, and had a higher incidence of comorbidities such as diabetes mellitus, CKD, hypercholesterolaemia, obesity, and congestive heart failure when compared with patients with non-resistant hypertension. They were also more likely to have established CAD, but not CVD or PAD, and more likely to have polyvascular disease.

Resistant hypertension and 4-year outcomes

After multivariate adjustment, patients with resistant hypertension had an 11% higher hazard of the primary endpoint of cardiovascular death/MI/stroke at 4 years, when compared with patients who had non-resistant hypertension (18.9 vs. 14.2%; HR: 1.11; 95% CI: 1.02–1.20; $P = 0.017$). This was likely due to differences in non-fatal stroke (6.9 vs. 5.3%; HR: 1.26; 95% CI: 1.10–1.45; $P = 0.0008$); CV death (9.8 vs. 6.9%; HR: 1.01; 95% CI: 0.90–1.14; $P = 0.83$); and rates of non-fatal MI were similar (4.6 vs. 3.7%; HR: 1.04; 95% CI: 0.88–1.22; $P = 0.69$). Rates of fatal strokes were also similar (1.8 vs. 1.2%; HR: 1.14; 95% CI: 0.86–1.50; $P = 0.36$). All cardiovascular hospitalizations were higher in patients with resistant hypertension (23.4 vs. 17.4%, OR = 1.18, 95% CI: 1.10–1.26; $P < 0.0001$), largely due to an increase in hospitalizations for congestive heart failure (12.6 vs. 6.2%, OR = 1.36, 95% CI: 1.23–1.51, $P < 0.0001$). Other outcomes including all-cause mortality were similar between the two groups. Outcomes were similar in patients with and without established atherothrombotic disease and in patients with single vascular or polyvascular disease (*Table 2*).

The above results were identical when medications were examined based on drug-class, rather than drug category (i.e. ACE-inhibitors and ARBs were considered to belong to one

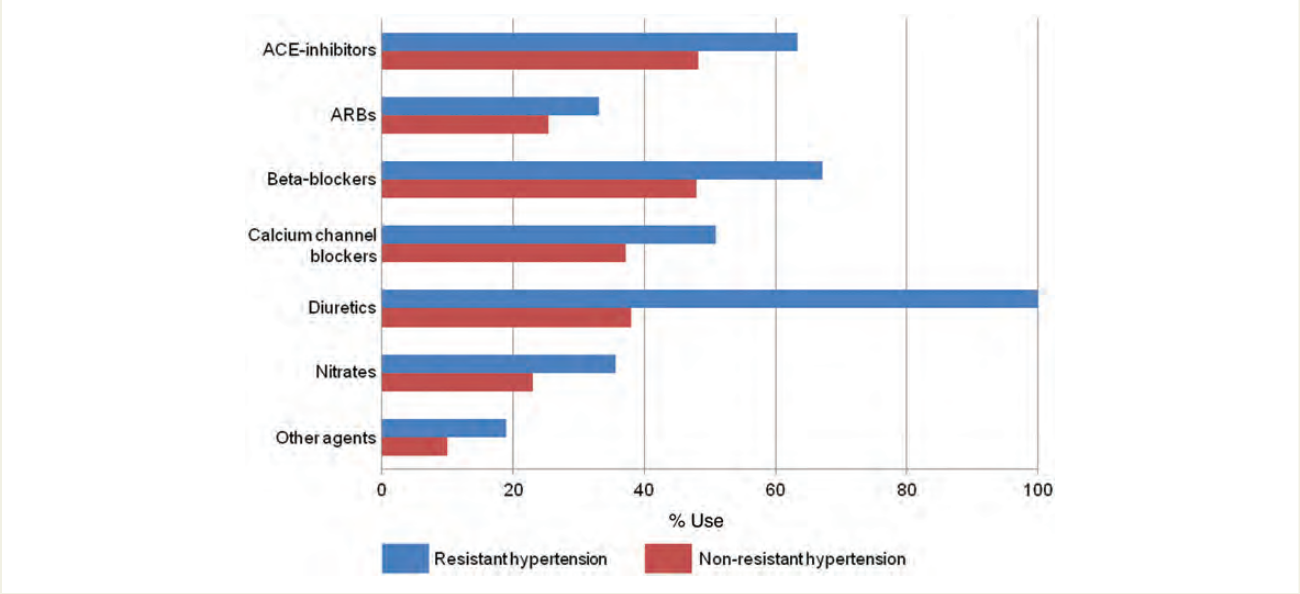

Figure 2 Antihypertensive medication use in patients with resistant and non-resistant hypertension. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

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Table 1 Baseline characteristics of the study population

Characteristic	Resistant hypertension ($n = 6790$)	Non-resistant hypertension ($n = 46\,740$)	*P*-value
Socio-demographic			
Age (years)	68.1 ± 9.6	69.1 ± 9.9	<0.0001
Female gender	44.2	37.9	<0.0001
Region			<0.0001
North America/Latin America/Western Europe/ Asia	75.4	79.6	
Eastern Europe/Middle East	21.5	8.5	
Japan/Australia	3.1	12.0	
Ethnicity			<0.0001
Caucasian	71.7	67.2	
Black	7.7	4.7	
Hispanic	4.8	4.9	
East/South Asian	5.6	15.0	
Other	10.2	8.2	
Systolic blood pressure (mmHg)	153.7 ± 17.1	138.1 ± 18.9	<0.0001
Diastolic blood pressure (mmHg)	89.0 ± 8.6	77.7 ± 11.0	<0.0001
Diabetes mellitus	65.2	44.4	<0.0001
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	40.1	28.3	<0.0001
Hypercholesterolaemia	75.1	73.7	0.013
Obesity (BMI ≥30 kg/m^2)	45.3	30.1	<0.0001
Current smoker	36.7	41.7	<0.0001
Heart failure	26.7	13.1	<0.0001
Atrial fibrillation	15.4	10.5	<0.0001
Established atherothrombosis	78.2	80.3	<0.0001
CAD	61.1	57.8	
CVD	28.7	28.2	
PAD	12.6	12.1	
Polyvascular disease	21.5	16.1	<0.0001
Laboratory values			
Serum creatinine (mg/dL)	1.2 ± 0.7	1.1 ± 0.7	<0.0001
Fasting blood glucose (mg/dL)	131.2 ± 50.5	120.8 ± 45.1	<0.0001
Fasting total cholesterol (mg/dL)	203.1 ± 52.9	191.4 ± 49.3	<0.0001
Fasting triglycerides (mg/dL)	181.4 ± 106.8	161.3 ± 95.9	<0.0001
Other medication history			
Aspirin	68.5	67.0	0.01
Statin	71.5	69.9	0.006
NSAIDs	13.6	12.1	0.0003

BMI, body mass index; eGFR, estimated glomerular filtration rate; NSAID, non-steroidal anti-inflammatory drug.
Numbers represent mean ± standard deviation for continuous variables, and % for binary or categorical variables. *P*-values were obtained with Student's *t*-test for continuous variables, and χ^2 test for categorical variables.

class). After the exclusion of nitrates from the definition of resistant hypertension, the overall prevalence of resistant hypertension decreased slightly to 11.8%. Adjusted multivariate outcomes for the primary endpoint were similar (18.3 vs. 14.3%; HR: 1.09; 95% CI: 1.001–1.19; $P = 0.047$).

Sensitivity analyses

When a conservative definition (baseline systolic BP ≥160 mmHg on ≥3 agents) was used for resistant hypertension, the overall prevalence decreased to 6.0%. This definition was still associated with a significant hazard for the primary endpoint in these patients

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Table 2 **Adjusted multivariate hazard ratios for 4-year outcomes in hypertensive patients with resistant vs. non-resistant hypertension**

Outcome	Hazard ratio (95% confidence intervals); *P*-value				
	All patients (*n* = 53 530)	**Established disease (*n* = 42 862)**	**Single vascular territory disease (*n* = 33 861)**	**Polyvascular disease (*n* = 9001)**	**Risk factors only (*n* = 10 668)**
CV death/ MI/stroke	1.11 (1.02–1.20), $P = 0.017$	1.10 (1.01–1.20), $P = 0.038$	1.10 (0.98–1.22), $P = 0.11$	1.04 (0.90–1.21), $P = 0.56$	1.32 (1.05–1.67), $P = 0.018$
CV death/ MI/stroke/CV rehospitalization[a]	1.18 (1.10–1.26), $P < 0.0001$	1.19 (1.11–1.28), $P < 0.0001$	1.16 (1.06–1.27), $P = 0.0011$	1.19 (1.04–1.36), $P = 0.01$	1.21 (1.01–1.46), $P = 0.043$
All-cause mortality	0.97 (0.88–1.07), $P = 0.55$	0.96 (0.87–1.07), $P = 0.47$	1.01 (0.88–1.14), $P = 0.93$	0.86 (0.72–1.03), $P = 0.10$	1.12 (0.87–1.44), $P = 0.38$
CV mortality	1.01 (0.90–1.14), $P = 0.83$	0.99 (0.87–1.12), $P = 0.86$	1.01 (0.86–1.19), $P = 0.87$	0.92 (0.75–1.13), $P = 0.43$	1.38 (0.99–1.91), $P = 0.06$
Non-fatal stroke	1.26 (1.10–1.45), $P = 0.0008$	1.28 (1.10–1.48), $P = 0.0011$	1.18 (0.97–1.43), $P = 0.10$	1.32 (1.05–1.66), $P = 0.018$	1.40 (0.95–2.08), $P = 0.089$
Fatal stroke	1.14 (0.86–1.50), $P = 0.36$	1.13 (0.84–1.53), $P = 0.41$	1.23 (0.83–1.81), $P = 0.30$	0.93 (0.58–1.49), $P = 0.77$	1.42 (0.67–3.00), $P = 0.36$
Non-fatal MI	1.04 (0.88–1.22), $P = 0.68$	1.08 (0.90–1.28), $P = 0.42$	1.08 (0.87–1.34), $P = 0.50$	1.02 (0.76–1.37), $P = 0.90$	0.87 (0.52–1.46), $P = 0.60$
Hospitalization due to CHF[a]	1.36 (1.23–1.51), $P < 0.0001$	1.39 (1.25–1.54), $P < 0.0001$	1.42 (1.25–1.63), $P < 0.0001$	1.29 (1.07–1.54), $P = 0.0066$	1.37 (1.03–1.83), $P = 0.029$

CHF, congestive heart failure; CV, cardiovascular; MI, myocardial infarction.

[a]Values represent multivariate adjusted odds ratios.

All models adjusted for gender, age, current smoker, history of diabetes, body mass index <20 (calculated as weight in kilograms divided by height in meters squared), timing of ischaemic event (no event, ≤1 year, >1 year), risk factors only vs. established disease, polyvascular disease vs. single-bed disease (where appropriate), baseline use of aspirin and statins, congestive heart failure, atrial fibrillation/flutter, Eastern Europe and Middle East vs. Japan and Australia vs. other regions, and chronic kidney disease.

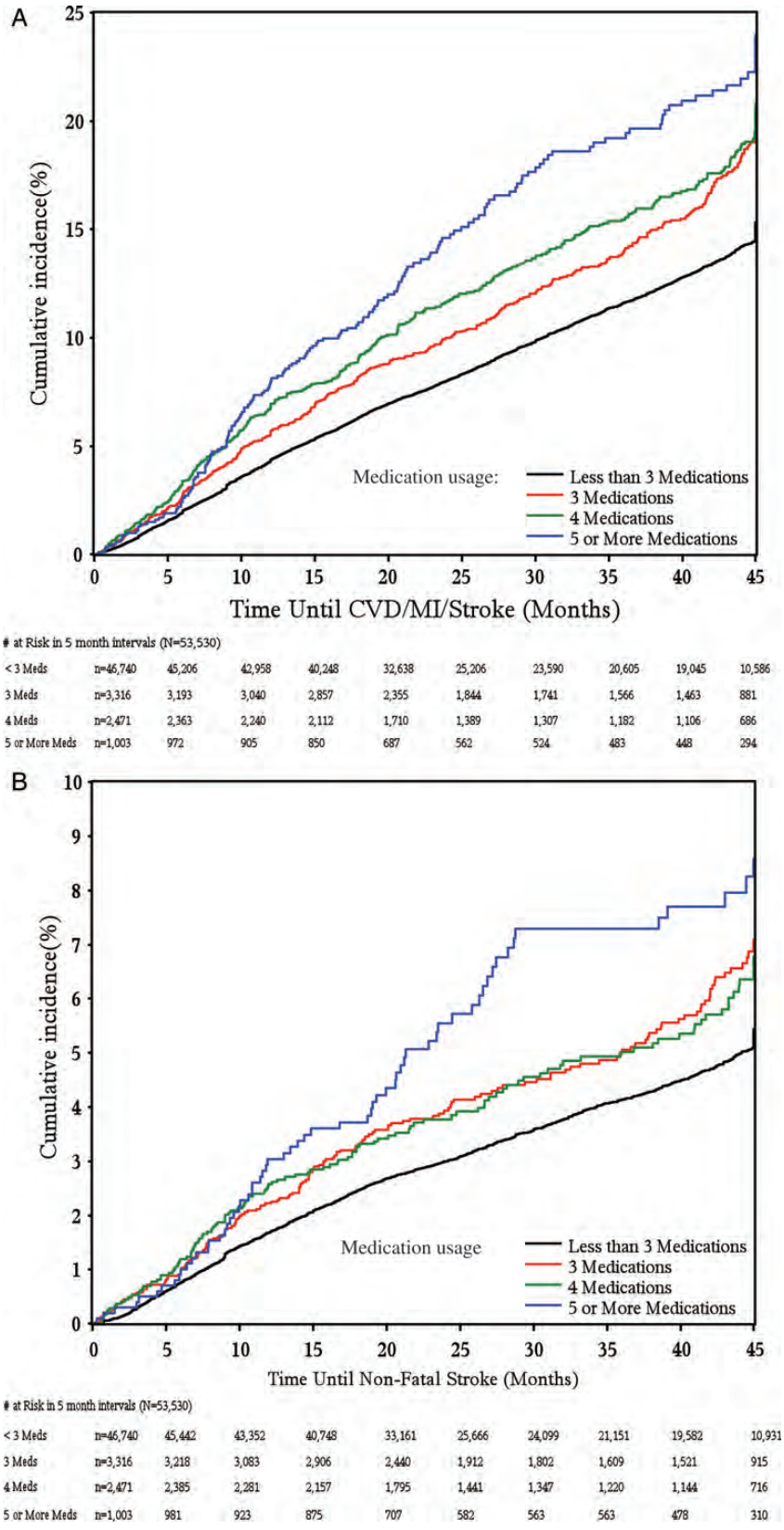

Figure 3. Cumulative hazard curves for the primary endpoint of cardiovascular death/myocardial infarction/stroke (*A*) and non-fatal stroke (*B*) in patients with non-resistant hypertension (<3 agents), resistant hypertension on three agents, resistant hypertension on 4 agents, and resistant hypertension on ≥5 agents ($P < 0.001$ for both curves by log-rank test).

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on multivariate adjusted analyses (19.1 vs. 14.6%; HR: 1.18; 95% CI: 1.06–1.32; $P = 0.003$).There was a stronger association with non-fatal stroke (HR: 1.52; 95% CI: 1.28–1.80; $P < 0.0001$); all other outcomes were similar to the primary definition. When the more liberal definition (uncontrolled on 3 agents, any BP on $\geq$4 agents) was implemented, the overall prevalence increased to 21.6%. Again, resistant hypertension was significantly associated with an elevated hazard of the primary endpoint (19.5 vs. 13.5%, HR: 1.16; 95% CI: 1.08–1.24; $P < 0.0001$). Interestingly, with this definition, resistant hypertension was associated with a significant increase in all cardiovascular endpoints, including all-cause mortality (HR: 1.11; 95% CI: 1.03–1.20; $P = 0.009$), cardiovascular mortality (HR: 1.17; 95% CI: 1.06–1.29; $P = 0.002$), non-fatal MI (HR: 1.23; 95% CI: 1.07–1.40; $P = 0.0032$), and heart failure hospitalizations (OR = 1.49; 95% CI: 1.36–1.62; $P < 0.0001$), but not non-fatal (HR: 1.04; 95% CI: 0.93–1.18; $P = 0.49$) or fatal (HR: 1.20; 95% CI: 0.95–1.53; $P = 0.13$) strokes.

Number of antihypertensive agents and 4-year outcomes

Mean baseline systolic and diastolic pressures in patients on <3, 3, 4, and $\geq$5 agents were 138.1 vs. 153.3 vs. 153.9 vs. 154.9 mmHg (P for trend <0.0001) and 77.7 vs. 88.9 vs. 89.0 vs. 89.5 mmHg (P for trend <0.0001), respectively. After multivariate adjustment, patients with resistant hypertension on 4 agents had a 15% higher hazard of the primary endpoint at 4 years, when compared with patients who had non-resistant hypertension (20.1 vs. 13.9%; HR: 1.15; 95% CI: 1.06–1.24; $P = 0.0004$). Similarly, patients with resistant hypertension on $\geq$5 agents had a 20% higher hazard of the primary endpoint (21.3 vs. 14.7%; HR: 1.20; 95% CI: 1.01–1.43; $P = 0.036$). Cumulative hazard curves for the primary endpoint and non-fatal strokes obtained by stratifying the patient population based on number of antihypertensive agents (<3, 3, 4, $\geq$5) are demonstrated in *Figure 3*. A dose–response relationship was noted, in that an increasing number of antihypertensive medications were associated with an increased risk for both these endpoints over 4 years (log-rank $P < 0.0001$ for both endpoints). On multivariate adjusted analyses, patients on $\geq$5 agents had a 21% increase in the risk for the primary endpoint when compared with those on $\leq$3 agents (HR: 1.21; 95% CI: 1.02–1.44; $P = 0.03$). After adjusting for baseline systolic and diastolic BPs, this relationship was somewhat attenuated (HR: 1.13, 95% CI: 0.95–1.35, $P = 0.16$).

Discussion

Our analysis of a large international observational registry of 53 530 patients with hypertension who either had established atherothrombotic disease or were at risk for developing it demonstrates that resistant hypertension is a frequent (prevalence: 12.7%) and ominous finding. It is associated with a significant increase in the risk of adverse cardiovascular outcomes in these patients, especially non-fatal stroke and congestive heart failure, by 4 years. A dose–response relationship with respect to the number of antihypertensive agents was also noted, with patients on $\geq$5 antihypertensive agents demonstrating a significant increase in adverse cardiovascular outcomes when compared with those on 3 agents. This is one of the largest prospective international registry analyses in patients with resistant hypertension, and to our knowledge, the only study in patients with resistant hypertension and either established atherothrombosis or risk factors for atherothrombosis.

Current prevalence estimates for resistant hypertension vary. Data from large clinical trials in hypertension suggest that as many as a third of patients were on $\geq$3 agents for BP control.[7,8] Two recent studies from the USA National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of resistant hypertension to be between 12.8 and 28% among treated hypertensive patients.[9,11] Although our study was not primarily designed as a survey to detect true prevalence rates, it suggests that the overall prevalence of resistant hypertension in patients with atherothrombotic disease may not be increased. Despite this, it is an important contributor to long-term adverse cardiovascular events, independent of other factors known to influence long-term outcomes such as age, gender, smoking, diabetes, body mass index, and use of medications such as aspirin and statins.[17] We note similar adverse outcomes in patients across the entire spectrum of atherosclerotic disease—from those with subclinical or asymptomatic disease to those with established single vessel and polyvascular disease. The increase in cardiovascular events was mainly due to a 26% increase in the risk of non-fatal strokes and a 36% increase in the risk of hospitalization for congestive heart failure by 4 years. We believe that these findings are an important addition to the field, since most outcomes studies in patients with resistant hypertension have been small and have lacked the power to discriminate between different cardiovascular causes of mortality and morbidity.[8,21]

Over the past few years, there has been significant interest in device-based therapies for the management of patients with resistant hypertension, including renal denervation via radiofrequency catheter ablation of renal sympathetic nerves and carotid baroreceptor activation therapy.[22–25] Our data are likely to be of significant interest to those either performing or looking to perform these procedures for a number of reasons. It outlines the global magnitude of the problem and describes commonly utilized medical therapies in a large community-based cohort. It is also one of the largest studies highlighting adverse long-term cardiovascular outcomes in these patients, and thereby highlights the potential salutary effects of these technologies. For this study, we defined resistant hypertension as uncontrolled BP $\geq$140/90 mmHg ($\geq$130/80 mmHg in diabetes and CKD). A more conservative definition (systolic BP $\geq$160 mmHg) is currently being employed by the SYMPLICITY HTN-3 (a renal denervation trial) investigators.[26] As expected, this decreases the eligible patient pool for the procedure (~6% of patients with atherosclerosis), but given the higher adverse event rate in this group, it suggests that the magnitude of benefit potentially achievable with these technologies may be quite large.[24] On the other hand, some groups advocate using a more liberal definition (BP $\geq$140/90 mm on 3 agents, any BP on 4 or more agents).[8] This would significantly increase the prevalence of resistant hypertension (one in five patients with atherosclerosis) but also underscores the large public health importance of this condition. Moreover, this definition brings out a very interesting finding in these patients. On the one hand, patients defined as having resistant hypertension

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by being poorly controlled on ≥3 agents mainly have a higher risk of stroke and congestive heart failure, more so than other cardiovascular endpoints. This is consistent with our current understanding of the direct association between elevated BP and stroke risk as well as heart failure risk, especially heart failure with preserved ejection fraction.[5,27,28] On the other hand, patients defined as having resistant hypertension by virtue of being on ≥4 antihypertensive agents (irrespective of BP control) also have a higher risk of all adverse cardiovascular outcomes (including all-cause mortality, cardiovascular mortality, myocardial infarction, and congestive heart failure), except stroke. In high-risk patients such as those with established atherothrombosis and/or diabetes, at least some of the elevation in risk could be due to a J-curve phenomenon, as recently highlighted by the ESH–ESC task force.[29] This particular observation is further corroborated by our finding of a dose–response relationship between the number of antihypertensive agents and adverse clinical outcomes. Thus, a higher number of antihypertensive medications, even with good BP control, may not ameliorate the long-term risk of adverse cardiovascular events. This is a novel finding, and highlights the urgent need for innovative approaches to management of resistant hypertension. To this effect, in addition to device-based therapies, newer pharmacological agents (including vaccine-based strategies) are being further evaluated.[22,25,30,31]

A major strength of the REACH registry is that it provides high-quality data (with a large sample size and with systematic audits and quality checks) with high follow-up rates and from diverse patient types and environments. Limitations of the REACH data are those inherent to registries such as selection bias (both patient and physician), and the presence of unmeasured confounders.[32] Another major limitation is the lack of information on medication dosing since optimal dosing constitutes an integral part of the definition of resistant hypertension, although earlier studies have used a definition identical to ours.[7,9–11] Moreover, guidelines refer to maximally tolerated/adequate doses which are different for each person.[5,6] However, in order to address this limitation, we conducted sensitivity analyses by varying the definition of resistant hypertension. Using a more conservative definition (only severely uncontrolled patients with SBP ≥160 mmHg) as well as a liberal definition (any BP control on ≥4 agents, thus reducing any misclassification bias) resulted in similar HRs for the primary endpoint. Another limitation is the lack of information regarding specific antihypertensive agents used. This was intentionally done at the time of designing the REACH registry to avoid *post hoc* (and likely confounded) head-to-head drug comparisons. However, information on drug class is available, and provides valuable information regarding commonly used drug types for hypertension management in a large international community-based cohort. Day-to-day patient adherence with the prescribed therapies also could not be assessed, although patient self-report has frequently been employed for similar analyses, and is the most useful method in the clinical setting.[33,34] It is possible that some patients labelled as having resistant hypertension in our study had either white-coat hypertension or pseudo-resistant hypertension due to conditions such as obstructive sleep apnoea, thyroid disease, renovascular disease, drug-induced hypertension, etc., and were thus misclassified.[7,35] Conversely, since our definition of resistant hypertension required the use of a minimum of three antihypertensive medications, we likely misclassified some patients with uncontrolled hypertension on one or two medications who would remain uncontrolled on ≥3 medications as having non-resistant hypertension. We also did not measure ambulatory BPs in these patients, which can provide valuable prognostic and diagnostic information in these patients.[8,36,37] Information on BP values at annual follow-up visits was also not available in the REACH registry. Based on the 2008 AHA statement, our definition of resistant hypertension incorporates BP control as a criterion for resistance.[8] However, this precludes us from assessing whether worse cardiovascular outcomes are due to resistant hypertension status itself or related to BP control.

Conclusion

Our analysis of a large international registry in stable outpatients with subclinical or established atherothrombosis demonstrates that resistant hypertension is a common finding and is associated with a significant increase in the long-term risk of adverse cardiovascular outcomes, especially non-fatal stroke and congestive heart failure. Greater efforts towards better BP control and novel strategies to improve BP control are required in this patient population.

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CARDIOVASCULAR FLASHLIGHT

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Regurgitation after Edwards SAPIEN valve implantation: truly paravalvular or 'supra-skirtal'?

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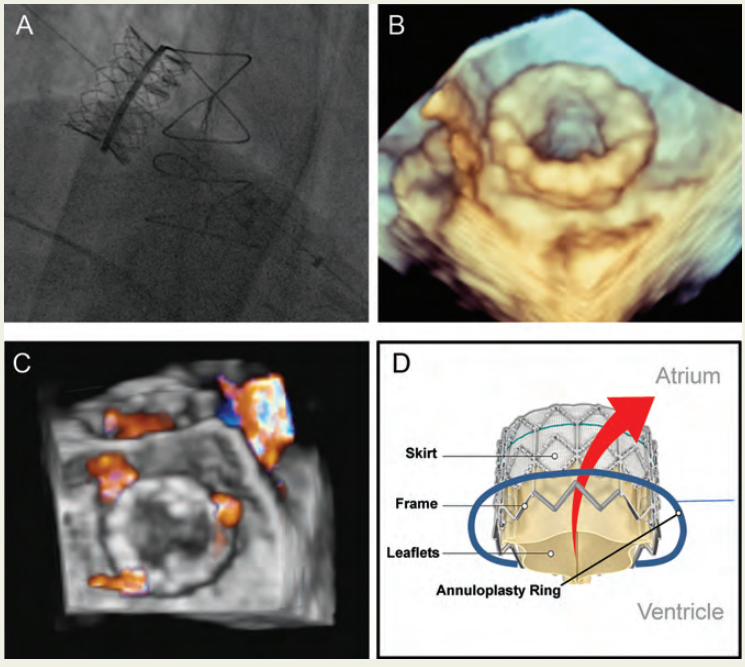
A 73-year-old male was referred with severe mitral regurgitation 9 years after mitral valve annuloplasty with a 32-mm Edwards Lifesciences ring. On the basis of an anticipated high perioperative risk related to chronic kidney disease and left ventricular systolic dysfunction, mitral valve-in-ring implantation using a 29-mm Edwards SAPIEN prosthesis was performed by transapical access (*Panel A*). Post-procedural three-dimensional transoesophageal echocardiography revealed three paravalvular regurgitation jets at the 3, 7, and the 11 o'clock positions (*Panels B* and *C*).



In this patient, we observed a third type of regurgitation in Edwards SAPIEN prostheses, which is caused by the device design. Edwards SAPIEN prostheses are built up by bovine pericardial tissue leaflets fixed on a stainless steel frame. A polyethylene terephthalate skirt partially covers the steel frame. However, since the skirt covers the basal two-thirds of the frame only, regurgitation through its uncovered part may occur (arrow, *Panel D*; adapted from www.edwards.com/products/transcathetervalve/Pages/sapienthv.aspx). This type of regurgitation was seen in the patient presented here, since the skirt is positioned in the left atrium rather than the annuloplasty ring. The commissures cover the whole length of the steel frame, and the regurgitation jets are therefore located in between the commissures and positioned ~120° apart from each other. In patients with Edwards SAPIEN prostheses in aortic position, the same phenomenon may be observed with prostheses implanted too apically. However, as the left ventricular outflow tract is narrow, regurgitation jets are more difficult to visualize.

Hence, after Edwards SAPIEN prosthesis implantation, regurgitation is transvalvular or paravalvular or 'supra-skirtal'. As the technology of transcatheter valves is still evolving, constant improvement in the device design and proper placement of the prosthesis are important.

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