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AMPD1 polymorphism and response to regadenoson

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Abstract

Aims—*AMPD1* c.34C>T (rs17602729) polymorphism results in AMPD1 deficiency. We examined the association of AMPD1 deficiency and variability of hemodynamic response to regadenoson.

Subjects & methods—Genotyping for c.34C>T was performed in 267 patients undergoing regadenoson cardiac stress testing.

Results—Carriers of c.34C >T variant exhibited higher relative changes in systolic blood pressure (SBP) compared with wild-type subjects ([%] SBP change to peak: 12 ± 25 vs 5 ± 13%; p = 0.01) ([%] SBP change to nadir: −3 ± 15 vs −7 ± 11%; p = 0.04). Change in heart rate was similar between groups, but side effects were more common in carriers of the variant (+LR = 4.2; p = 0.04).

Conclusion—AMPD1 deficiency may be involved in the modulation of regadenoson's systemic effects.

Keywords

adenosine; genetic; myocardial perfusion imaging; regadenoson

AMPD1 c.34C>T (rs17602729) is a polymorphism present in 12–18% of Caucasians and 19% of African–Americans [1,2]. This variant results in the substitution of cytosine for thymidine, leading to a premature stop codon and substantially diminished enzymatic function [2,3]. AMPD1 deficiency leads to reduced clearance of adenosine monophosphate

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

(AMP) and increased production of adenosine in skeletal muscles. The heterozygous population exhibits partial enzymatic deficiency. Although carriers of this variant are frequently asymptomatic and phenotypically similar to wild types (CC), carrier status, both homozygous (TT) and heterozygous (CT) has been associated with myalgias or weakness after prolonged exercise [4] and increased blood flow response to sprint exercise [5].

Adenosine has been the principle agent used in pharmacological cardiac stress tests due to its effects on coronary vasodilation. By stimulating adenosine A2A receptors on arteriolar vascular smooth muscle cells, adenosine induces coronary arterial vasodilation and myocardial hyperemia, the desired cardiac state for myocardial perfusion imaging (MPI). The nonselective activation of A1, A2B and A3 receptors by adenosine, however, can lead to adverse effects including nausea, chest pain, dyspnea and less commonly, bronchospasm and heart blocks [6,7]. In 2008, regadenoson, an adenosine analogue and selective A2A adenosine receptor agonist was approved by the US FDA [8]. Regadenoson has since rapidly replaced adenosine during MPI because of desirable factors including a longer half-life, uniform dosing and ease of administration as a rapid bolus. In contrast to adenosine, regadenoson achieves myocardial hyperemia quicker and maintains it longer, attributes that make it optimal for radionuclide MPI [9]. Adenosine causes a sympathetic increase in the heart rate (HR), and systolic blood pressure (SBP), along with a drop in the diastolic blood pressure [10]. Factors that exacerbate or mitigate this physiologic response have been poorly studied.

The effects of genetic polymorphisms on variation in response to *in vivo* administration of regadenoson have not been studied. We hypothesized that carriers of the *AMPD1* c.34C>T variant allele linked to AMPD1 deficiency exhibit an altered hemodynamic response to A2A receptor stimulation by regadenoson.

Subjects & methods

Patients

The study protocol was approved by the Indiana University institutional review board. Written informed consent was obtained from all participants.

Subjects who were scheduled for resting regadenoson nuclear stress testing were eligible to be enrolled in this study. Subjects who underwent a combination of exercise and nuclear pharmacologic stress testing with regadenoson were excluded from analysis. Data on demographics, medical history, family history, risk factors and dietary history were collected.

Genotyping

Genomic DNA was extracted by using the Qiagen Flexigene DNA Kit #51206 following the protocol for isolation of DNA from 100–500 μl buffy coat (Germantown, USA). *AMPD1* c. 34C>T (rs17602729) was analyzed using an open array genotyping platform (Life Technologies, NY, USA) according to the manufacturer's instructions. Alleles of interest were amplified by using sequence-specific primers as well as two allele-specific TaqMan®

probes (Applied Biosystems, CA, USA). Allelic discrimination was used to determine individual genotypes.

Regadenoson administration

A standard dose of 0.4 mg of regadenoson was administered through a peripheral intravenous line over a period of 10 s, followed by a saline flush of 5 ml over another 10 s.

Study measurements

Hemodynamic parameters, including SBP and HR, were measured prior to regadenoson infusion, then at 1 min intervals over a period of 5 min thereafter. Self-reported side effects were recorded. Primary outcomes were [1] change in HR [2], change in SBP to peak (both absolute and relative [%]) and [3] change in SBP to nadir (both absolute and relative [%]) postregadenoson administration. Change in HR was defined as the difference between the peak postadministration HR and the HR prior to regadenoson administration (baseline HR). Absolute change in SBP to peak was defined as the difference between the peak postadministration SBP and the baseline SBP. Likewise, absolute change in SBP to nadir was defined as the difference between the nadir postadministration SBP and the baseline SBP. Percentage [%] change was calculated by dividing the absolute change by the baseline SBP and multiplying the result by a 100. Secondary outcomes included the incidence of side effects reported by patients (nausea, abdominal pain, chest pain, dyspnea, dizziness, flushing and headache).

Statistical analysis

Statistical analyses were performed by using SPSS software, version 21.0 (IBM, IL, USA). Statistical significance was defined as p-value of less than 0.05. All statistical tests were two-sided, and values are represented as the mean ± standard deviation, unless otherwise indicated. Unpaired two-sided Student's *t*-test was used to compare normally distributed continuous variables. Categorical variables were compared by using the chi-square test. *AMPD1* genotypes (CC and CT + TT) were included in forward stepwise multivariate linear regression analysis, along with clinical variables associated with $p < 0.1$ in univariate analysis.

Results

The study population consisted of 267 individuals who underwent regadenoson stress testing, 55% of whom were females. The mean age was 58 years, and the majority was Caucasian [72.0%]. Baseline patient characteristics are summarized in Table 1. Two patients were homozygous for the *AMPD1* T variant allele, 40 were heterozygous and 225 were wild type. Distribution of genotypes was consistent with Hardy–Weinberg equilibrium ($p > 0.05$). Carriers of the T allele, including homozygous and heterozygous individuals, were analyzed as a single group, and compared with the wild-type group, unless otherwise indicated.

There was no significant difference in baseline, peak and nadir SBP, and baseline and peak HR in the CT + TT group when compared with the CC group (Figure 1). The relative rise in SBP (% SBP change to peak) was significantly higher in the carrier group as compared with

the wild-type group (12 ± 25 vs 5 ± 13%; p = 0.01) (Figure 2A), as was the absolute rise in SBP (SBP change to peak: 14 ± 28 vs 6 ± 18 mm; p = 0.02) (Figure 2C). There was no significant difference in the absolute drop in SBP (SBP change to nadir: −11 ± 17 vs −5 ± 18 mm; p = 0.08) between both groups (Figure 2C), but the relative decrease in SBP was significantly different (% SBP change to nadir: −7 ± 11 vs −3 ± 15%; p = 0.04) (Figure 2A). HR change did not differ significantly (31 ± 14 vs 30 ± 14 bpm; p = 0.6). In a multivariate linear regression analysis, age, gender, hyperlipidemia and smoking significantly affected the association between [%] SBP change to peak and *AMPD1* genotype (Table 2). The same variables, with the exception of smoking, affected the absolute SBP change to peak (Table 2), while both relative and absolute SBP change to nadir were only affected by age (Table 2). After accounting for confounding variables, T allele carriers remained significantly associated with a more elevated [%] change in SBP to peak (p = 0.009) (Table 2) and with a lesser decrease in [%] SBP change to nadir (p = 0.044) (Table 2). The absolute SBP change to peak continued to be significant (p = 0.012) (Table 2), while the absolute SBP change to nadir remained nonsignificant (p = 0.061) after multivariate adjustment (Table 2). Multivariate linear regression analysis of HR change and *AMPD1* genotype demonstrated significant association of previous percutaneous coronary intervention (PCI), systolic heart failure, age and gender with HR change (Table 2). After adjustment of significant covariates, *AMPD1* c.34C>T polymorphism was not significantly associated with mean HR change (p = 0.554).

Secondary outcomes measured included the incidence of side effects after regadenoson administration. Side effects reported by patients included nausea, abdominal pain, chest pain, dyspnea, dizziness, flushing and headache. Subjects were categorized in two groups: [1] no side effects reported and [2] one or more side effects reported. The incidence of side effects was significantly increased in carriers (CT + TT) as compared with the wild-type group (CC) (39/42 [93%] vs 182/225 [81%]; likelihood ratio [+] = 4.2; p = 0.04; odds ratio = 3.1; 95% CI: 0.91–10.4) (Figure 3). There was an increased incidence of all side effects except chest and abdominal pain in the carrier group. The incidence of side effects increased with every additional T allele, exhibiting a gene-dose effect (Figure 3).

Discussion

AMPD1 mediates the transformation of AMP into inosine monophosphate in the cytosol of skeletal muscle cells. Catalysis by AMPD1 plays an important role in the purine salvage nucleotide cycle and is a crucial step in the regeneration of energy during states of ischemia. In response to hypoxic states, tissue cells become dependent on oxidative phosphorylation in an attempt to meet increasing energy demands. This results in an increased production of AMP, which is in turn dephosphorylated by 5’-nucleotidase to form adenosine [2]. Adenosine has both direct and indirect downstream effects. By inducing smooth muscle relaxation and coronary arterial vasodilation via A2A receptor binding, adenosine improves blood flow and oxygen delivery [2,11]. Stimulation of A1 receptor by adenosine induces negative inotropy and chronotropy, thereby minimizing oxygen demand [2,9]. In addition to these direct vasomotor effects, adenosine stimulates carotid-body chemoreceptors and sympathetic afferent nerves resulting in systemic vasoconstriction. This complex mechanism leads to an overall increase in blood pressure and HR [10].

AMPD1 c.34C>T is a common genetic polymorphism, found in 12–18% of Caucasians, 2% of whom are homozygous [1,2] and leads to functional AMPD1 deficiency. Lack of AMPD1 in skeletal muscles reduces the ability to regenerate ATP stores, and may therefore result in decreased exercise capacity and symptoms of muscle fatigue [12,13]. Forearm blood flow in response to transient ischemia is increased significantly in T variant allele carriers when measured using venous occlusion plethysmography [14]. Femoral artery blood flow measured by ultrasonography is also increased in subjects with AMPD1 deficiency during cycling sprint exercise with more rapid recovery postexercise, but lower peak power, as compared with normal subjects, an effect that has been attributed to an AMPD1-dependent increase in adenosine formation during exercise [5]. Sabina *et al.* reported a 16-fold increase in postexercise adenosine levels in muscle biopsies obtained from subjects with AMPD1 deficiency compared with a twofold increase in controls [12]. Consistent with these findings, lower prevalence of *AMPD1* T variant allele has been documented in top-level endurance athletes as compared with controls [1,15].

In this study, we examine the effects of regadenoson on SBP and HR among patients that carry the T variant allele in the context of pharmacologic cardiac stress testing. We found that in response to regadenoson, carriers (CT + TT) exhibited a higher relative rise in SBP at its peak and a smaller relative drop in SBP at its lowest measurement. However, HR changes did not differ between both groups (31 ± 14 vs 30 ± 14 bpm; $p = 0.6$). Since absolute changes in SBP are affected by baseline measurements of SBP, the use of relative [%] SBP change allows adjustment for the differences in the baseline measurements. It is therefore likely a more accurate reflection of the magnitude of change in SBP, whether to peak or to nadir. Among T allele carriers, we observed a significant difference in SBP change in response to regadenoson, with higher relative rise in SBP and a smaller relative drop in SBP. In view of the complex effects of adenosine and its analogues, multiple mechanisms may explain this observation. Activation of A2A receptors triggers a state of hyperemia in the myocardium and induces sympathetic excitation [9]. AMPD1 is present in both skeletal muscle cells [16], as well as myocardium [17], and could therefore influence the A2A-mediated response during MPI. Kalsi *et al.* have demonstrated decreased AMPD activity in human myocardium harvested at time of left ventricular assist device implantation or heart transplant in T allele carriers with advanced heart failure as compared with wild-type controls [18]. Klinger *et al.* described two potential mechanisms involved in the vasodilatory effect of adenosine on endothelial cells. The binding of adenosine to A2A receptors on endothelial cells may trigger an internal signaling pathway that activates nitric oxide synthase, resulting in increased vasodilation. Adenosine is also thought to have an additional direct vasodilatory effect on arterial smooth muscle cells [11]. Sympathetic activation causes peripheral vasoconstriction, triggering augmented local endogenous adenosine production in response to a state of increased demand. In addition, stimulation of A2A receptors in atrial myocytes results in ryanodine receptor phosphorylation, and release of Ca^{2+} from sarcoplasmic reticulum, possibly contributing to the rise in HR consistently observed with regadenoson administration [19,20].

AMPD1 deficiency leads to accumulation of intracellular AMP during hypoxia. Increase in AMP/ATP ratio has been demonstrated to result in activation of AMP-activated protein kinase during hypoxia and result in pulmonary vasoconstriction [21]. While not previously

studied, alteration of AMP-activated protein kinase activity could occur in AMPD1-deficient subjects, and possibly influence the vasoactive response to A2A stimulation in vascular smooth muscle cells. Activation of AMP-activated protein kinase has been shown to inhibit nitric oxide-mediated aortic vascular smooth muscle cell relaxation [22]. Variability in peripheral vasoconstriction may in part explain the increase in SBP without significant difference in HR response among AMPD1-deficient subjects.

The HR response was not significantly different across the different *AMPD1* genotypes, possibly because the resulting tachycardia is predominantly influenced by ryanodine receptor activation in the sinus nodal tissue.

The majority of adenosine's side effects are thought to be secondary to its vasodilatory properties on vessels of the skin, brain and abdominal viscera, leading to flushing, nausea, headache and abdominal pain respectively [23]. In our study, we demonstrate a higher rate and higher likelihood for the occurrence of side effects from regadenoson administration in T allele variant carriers as compared with wild-type individuals. Interestingly, the order of side effect incidence was identical in both groups, with dyspnea, dizziness and flushing (in descending order) being the most common (Figure 3). Increased incidence of adenosine-specific side effects with *in vivo* administration of exogenous adenosine analogues in AMPD1-deficient patients may be the result of adenosine accumulation and activation of non-A2A adenosine receptors.

With regards to the FDA warning issued in November 2013 concerning the increased incidence of fatal myocardial infarction in patients receiving regadenoson or adenosine for cardiac nuclear stress tests, our study population, whether carriers of the c.34C>T mutation or wild type for that polymorphism, had no occurrences of adverse myocardial infarction. Continuous monitoring of electrocardiograms during regadenoson stress testing did not show any instances of AV nodal blockade in all the subjects tested.

Limitations of our study include a small number of homozygous individuals for c.34C>T and various co-morbidities that could account for unadjusted confounding in our analysis. The disparity in the racial groups (Caucasian and African–American) between carriers and noncarriers of the T allele is likely related to their prevalence in our geographic location, and the prevalence of the carrier state in general. Additionally, race was included in the multivariate analysis and did not significantly affect hemodynamic response (both SBP and HR). Further studies will be required before conclusions can be drawn whether pretest determination of *AMPD1* genotype would be helpful prior to performance of regadenoson stress testing, in specific further analysis of whether altered response to regadenoson influences the sensitivity or specificity of pharmacologic MPI in diagnosis of coronary ischemia.

Conclusion

Regadenoson has become the predominantly used agent in pharmacologic MPI, yet its interplay with native adenosine metabolism is incompletely understood and merits further investigation. Our study suggests that carriers of the *AMPD1* c.34C>T variant exhibit an

exaggerated response to regadenoson and demonstrate an increased likelihood of adverse side effects. Further studies are needed to elucidate the association of *AMPD1* variants and the phenotypic response to regadenoson stress testing, as well as sensitivity and specificity of MPI.

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Executive summary

- Common genetic polymorphisms may play a role in the hemodynamic response to regadenoson during cardiac stress testing.
- AMPD1 deficiency resulted in an altered systemic response to regadenoson, with the involved subjects exhibiting higher SBP after regadenoson administration.
- Carriers of the *AMPD1* T variant allele were more likely to develop side effects after regadenoson administration.

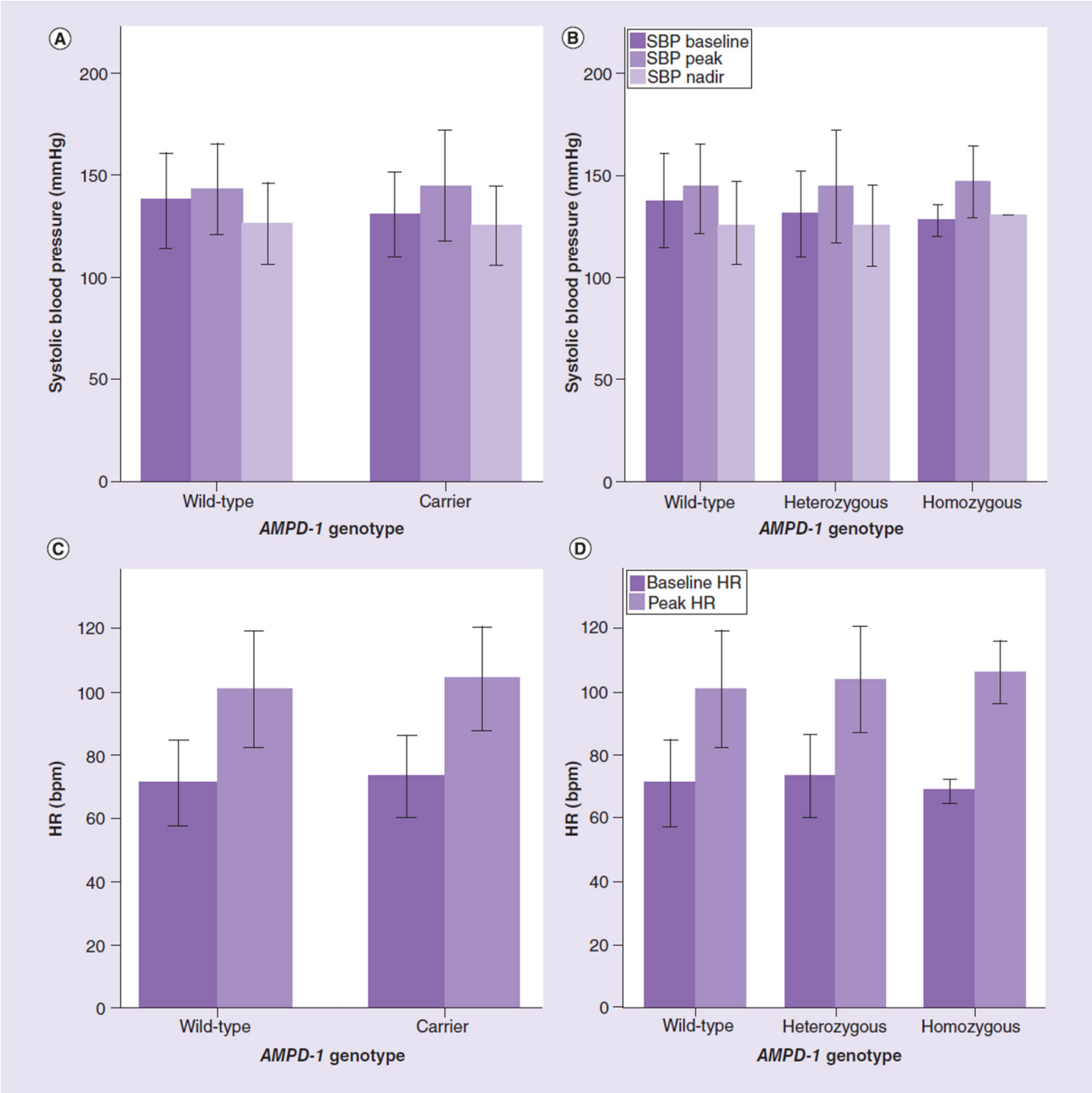

Figure 1. Systolic blood pressure and heart rate response to regadenoson

(A) SBP at baseline, peak and nadir in wild-type and carrier groups. **(B)** SBP at baseline, peak and nadir in wild-type, heterozygous and homozygous groups. **(C)** Baseline HR and peak HR in wildtype and carrier groups. **(D)** Baseline HR and peak HR in wild-type, heterozygous and homozygous groups.

HR: Heart rate; SBP: Systolic blood pressure.

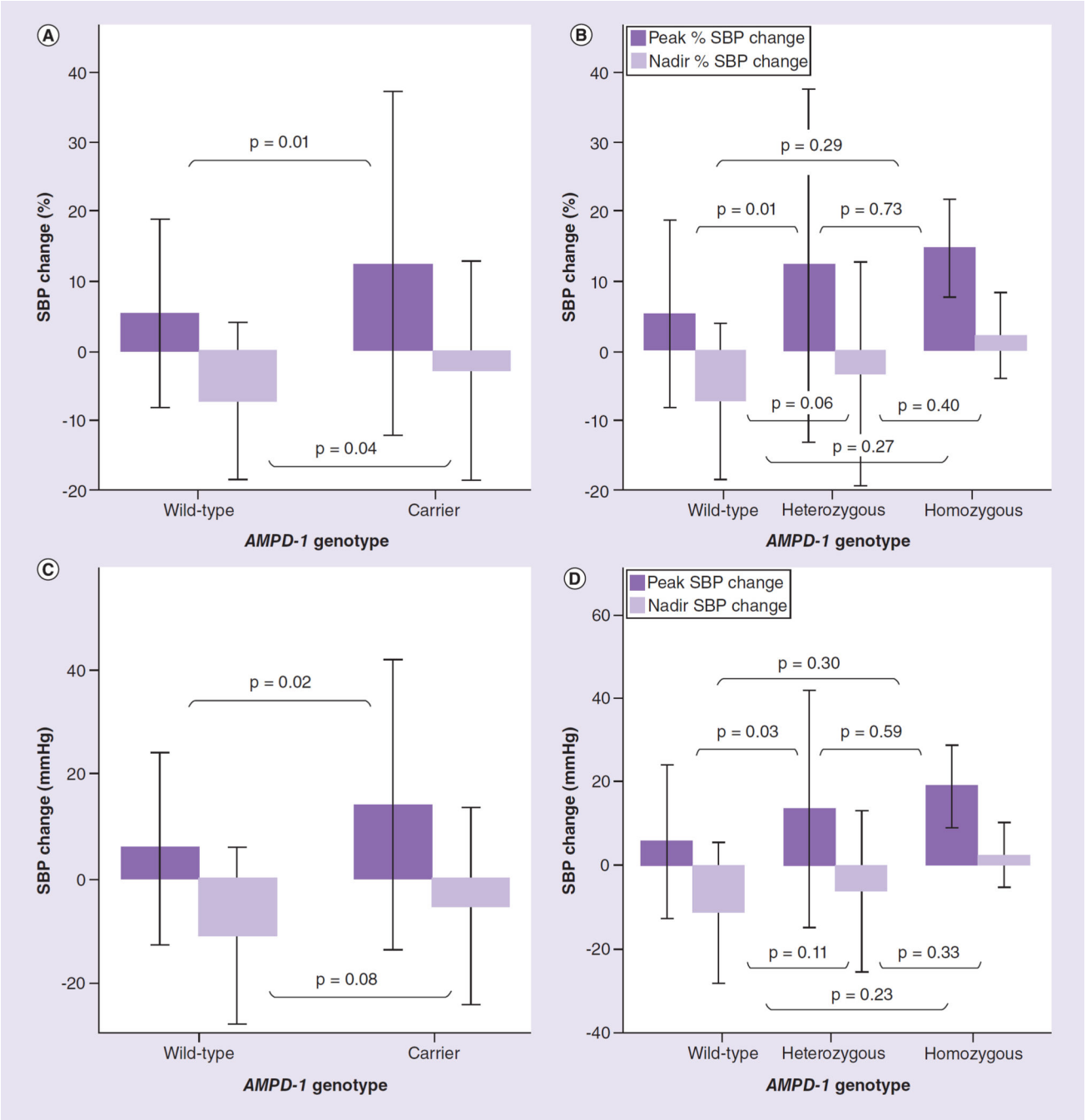

Figure 2. Absolute and percentage systolic blood pressure change in response to regadenoson

(A) Percentage SBP change to peak and nadir in wild-type and carrier groups. **(B)** Percentage SBP change to peak and nadir in wild-type, heterozygous and homozygous groups. **(C)** Absolute SBP change to peak and nadir in wild-type and carrier groups. **(D)** Absolute SBP change to peak and nadir in wild-type, heterozygous and homozygous groups. SBP: Systolic blood pressure.

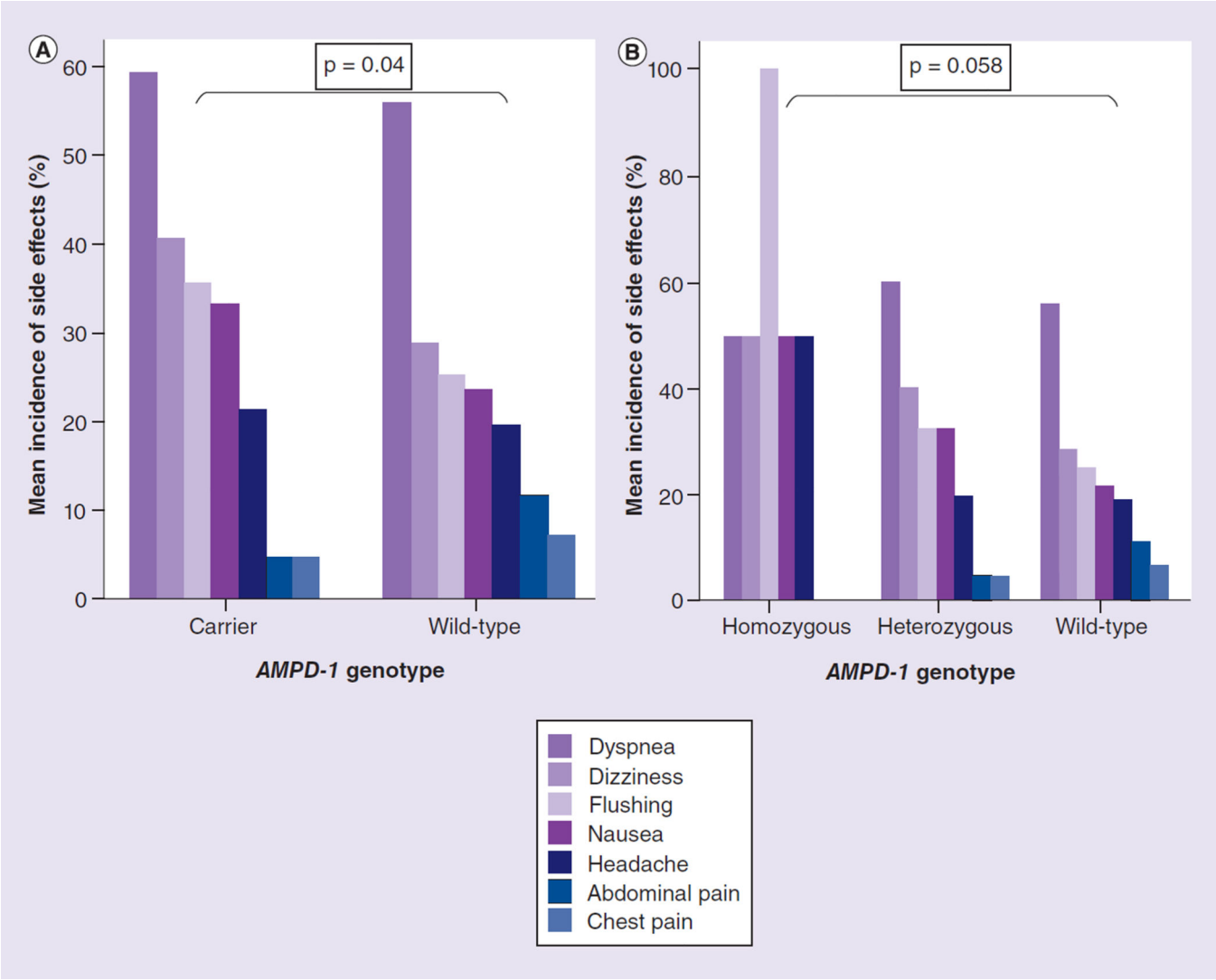

Figure 3. Incidence of side effects following regadenoson administration

(A) Incidence of side effects following regadenoson administration in carrier and wild-type groups. **(B)** Incidence of side effects following regadenoson administration in homozygous, heterozygous and wild-type groups.

Table 1

Baseline characteristics.

Characteristics	Total (n = 267)	Wild-type (CC), (n = 225)	Carrier (CT + TT), (n = 42)	Heterozygous (CT), (n = 40)	Homozygous (TT), (n = 2)	p-value (CC vs CT + TT)	p-value (CC vs CT vs TT)
Mean age (years)	58.4	58.6	57.2	57	61.1	0.54	0.39
Mean BMI (kg/m^2)	35	35	34.9	35.2	28.2	0.36	0.15
Males	120/267 (44.9%)	103/225 (45.8%)	17/42 (40.5%)	16/40 (40%)	1/2 (50%)	0.53	0.79
Females	147/267 (55.1%)	122/225 (54.2%)	25/42 (59.5%)	24/40 (60%)	1/2 (50%)	0.53	0.79
Race							
Caucasian	192/267 (72.0%)	156/225 (69.3%)	36/42 (85.7%)	34/40 (85%)	2/2 (100%)	0.03	0.09
African–American	71/267 (26.6%)	67/225 (39.8%)	4/42 (9.5%)	4/40 (10%)	0/2 (0%)	0.01	0.02
Others	4/267 (1.5%)	2/225 (1.0%)	2/42 (4.8%)	2/40 (5%)	0/2 (0%)	0.06	0.44
Coffee drinker	211/265 (79.6%)	178/225 (79.1%)	33/42 (78.6%)	31/40 (77.5%)	2/2 (100%)	0.88	0.77
Smoking	87/265 (32.8%)	71/225 (31.6%)	16/42 (38.1%)	16/40 (40%)	0/2 (0%)	0.36	0.32
Hyperlipidemia	182/267 (68.2%)	150/225 (66.7%)	32/42 (76.2%)	30/40 (75%)	2/2 (100%)	0.23	0.36
Coronary artery disease	82/267 (30.7%)	65/225 (28.9%)	17/42 (40.5%)	15/40 (37.5%)	2/2 (100%)	0.14	0.06
Prior PCI	58/267 (21.7%)	46/225 (20.4%)	12/42 (28.6%)	12/40 (30%)	0/2 (0%)	0.24	0.3
Prior CABG	25/267 (9.4%)	19/225 (8.4%)	6/42 (14.3%)	5/40 (12.5%)	1/2 (50%)	0.23	0.1
Hypertension	215/267 (80.5%)	180/225 (80.0%)	35/42 (83.3%)	33/40 (82.5%)	2/2 (100%)	0.62	0.73
Congestive heart failure	29/267 (10.9%)	24/225 (10.7%)	5/42 (11.9%)	5/40 (12.5%)	0/2 (0%)	0.81	0.83
Diabetes mellitus	111/267 (41.6%)	93/225 (41.3%)	18/42 (42.9%)	17/40 (42.5%)	1/2 (50%)	0.86	0.96

Characteristics	Total (n = 267)	Wild-type (CC), (n = 225)	Carrier (CT + TT), (n = 42)	Heterozygous (CT), (n = 40)	Homozygous (TT), (n = 2)	p-value (CC vs CT + TT)	p-value (CC vs CT vs TT)
Chronic kidney disease	10/267 (3.7%)	9/225 (4.0%)	1/42 (2.4%)	1/40 (2.5%)	0/2 (0%)	0.61	0.87
Peripheral vascular disease	37/267 (13.9%)	32/225 (14.2%)	5/42 (11.9%)	4/40 (10%)	1/2 (50%)	0.69	0.29
Stroke	27/267 (10.1%)	26/225 (11.6%)	1/42 (2.4%)	1/40 (2.5%)	0/2 (0%)	0.07	0.19
Beta blocker	126/267 (47.2%)	104/225 (46.2%)	22/42 (52.4%)	20/40 (50%)	2/2 (100%)	0.61	0.57
Calcium channel blocker	74/267 (27.7%)	64/225 (28.4%)	10/42 (23.8%)	10/40 (25%)	0/2 (0%)	0.54	0.62
ACE inhibitor	126/267 (47.2%)	110/225 (48.9%)	16/42 (38.1%)	15/40 (37.5%)	1/2 (50%)	0.41	0.76

ACE: Angiotensin-converting enzyme; CABG: Coronary arteries bypass grafting; PCI: Percutaneous coronary intervention.

Table 2

Multivariate analyses of systolic blood pressure and heart rate.

Hemodynamic response to regadenoson	Variable	Effect size	CI	p-value
Percentage SBP change to peak	*AMPD1* (CT + TT)	7.02	(1.78–12.26)	0.009
	Age	−0.26	(−0.44 to −0.07)	0.007
	Male gender	−5.39	(−9.13 to −1.64)	0.005
	Hyperlipidemia	−4.44	(−8.61 to −0.27)	0.037
	Smoking	4.041	(0.01–8.08)	0.05
Absolute SBP change to peak	*AMPD1* (CT + TT)	8.7	(1.95–15.46)	0.012
	Age	−0.32	(−0.55 to −0.08)	0.018
	Male gender	−6.05	(−10.88 to −1.26)	0.014
	Hyperlipidemia	−6.58	(−11.92 to −1.24)	0.016
Percentage SBP change to nadir	*AMPD1* (CT + TT)	4.18	(0.11–8.24)	0.044
	Age	−0.21	(−0.35 to −0.07)	0.004
Absolute SBP change to nadir	*AMPD1* (CT + TT)	5.58	(−0.27–11.42)	0.061
	Age	−0.29	(−0.49 to −0.09)	0.005
HR change	*AMPD1* (CT + TT)	1.31	(−3.04–5.65)	0.554
	Age	−0.21	(−0.36 to −0.05)	0.008
	Male gender	−4.15	(−7.32 to −0.98)	0.011
	Systolic heart failure	−7.48	(−12.49 to −2.48)	0.004
	Prior PCI	−5.35	(−9.21 to −1.49)	0.007

HR: Heart rate; PCI: Percutaneous coronary intervention; SBP: Systolic blood pressure.