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PERSONALIZED THERAPY IN CARDIOLOGY: THE ROLE OF PHARMACOGENETICS AND BIOMARKERS IN THE SELECTION OF ANTIHYPERTENSIVE AND ANTIPLATELET AGENTS - POTENTIAL AND LIMITATIONS OF IMPLEMENTATION

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ABSTRACT

The introduction of pharmacogenetic testing in the selection of pharmacotherapy can help optimize the choice of drugs to achieve better treatment results in patients by increasing the effectiveness of therapy and preventing undesirable side effects.

The aim of the work is to determine which pharmacogenetic tests and clinical biomarkers are already changing

The study provides an analytical review with elements of secondary quantitative synthesis. For sources with available outcome frequencies, absolute risk differences and approximate NNT values are additionally calculated.

The most mature implantation zone was identified for CYP2C19 when choosing P2Y12 inhibitors after acute coronary syndrome and PCI. In carriers of alleles with reduced function, clopidogrel works less effectively, whereas switching to ticagrelor or prasugrel can reduce the ischemic residual risk.

Rather than broad genetic panels, biomarkers of phenotype and safety, such as plasma renin activity, aldosterone/renin ratio, albuminuria, eGFR, and potassium, are more useful in antihypertensive therapy. Personalization already provides the greatest impact where the marker is integrated into a short prescribing algorithm and is available on time, coinciding with the speed of the clinical solution.

The limiting factors remain the ethnic heterogeneity of the results, the organizational cost of testing, and the lack of uniform algorithms for most antihypertensive pharmacogenetic signals.

KEYWORDS: personalized therapy, cardiology, pharmacogenetics, CYP2C19, clopidogrel, hypertension, biomarkers, plasma renin activity, albuminuria, antiplatelet agents.

INTRODUCTION

Personalized medicine appeared about three decades ago. Even then, many scientists, researchers, and doctors were interested in it. However, it was only after the complete discovery of the human genome in 2001 that personalized medicine began to provide an opportunity for certain pathologies (oncology, rheumatology, cardiology) to select the most effective treatment with minimal adverse drug reactions for a particular patient [3]. The ability to possess genetic information provides a chance to suspect, predict, and predict the onset of a disease. Personalized medicine is able in some cases to tell for sure whether a drug will work for a given patient, bringing us closer to "treating not the disease, but the patient" [5].

The ability to possess genetic information has allowed the introduction of personalized medicine into clinical practice. Genetic studies have begun to show that certain medications are very effective for some patients under certain conditions and ineffective, and sometimes even dangerous, for others [10]. Therefore, pharmacogenetics emerged at the junction of pharmacology and genetics, a science that studies the role of genetic factors in the formation of the pharmacological response of the human body to a drug [1]. This may enable the doctor to choose both the medicine itself and the dose for a particular patient in a personalized manner and ensure maximum effectiveness and safety of the drug.

The same treatment regimens in cardiac patients often give different results. One patient on clopidogrel undergoes an early post-intervention period without ischemic complications, while the other remains at high residual risk of thrombosis. A similar situation can be seen in antihypertensive therapy: with similar baseline pressure figures, one patient responds to a thiazide diuretic quickly, while the other requires several drug permutations and still remains outside the target values [11].

For a long time, these differences were attributed mainly to adherence, age, comorbidity, and drug interactions. This view has not disappeared, but it has already become too narrow. It is noteworthy that the biological heterogeneity of the response has at least two dimensions: a genetically determined metabolic rate or sensitivity to the drug and the current phenotype of the disease, which is reflected by laboratory parameters, markers of damage to target organs, parameters of kidney function and features of neurohumoral activation [12].

If we compare antiplatelet and antihypertensive therapy, the difference in the maturity of the personalized approach becomes almost obvious. There is already a clear decision-making axis for P2Y12 inhibitors - CYP2C19 and clopidogrel. In hypertension, dozens of genetic associations are associated with a much more modest number of really working clinical algorithms, and the daily choice of a drug is most often determined by the level of albuminuria, kidney function, suspicion of a sodium-dependent variant of the disease and the risk of hyperkalemia [8].

This leads to a practical difficulty. There are more publications, but the number of markers that actually change a doctor's prescription for a particular patient is growing much more slowly. As the analysis of recent studies shows, it is more productive to ask not about the "gene–drug" relationship itself, but about whether knowledge of the marker leads to a different choice of medicine and whether this changes the outcome. This is where the boundary between biological plausibility and clinical tool lies.

MATERIALS AND METHODS OF RESEARCH

The work is performed as an analytical review with elements of secondary quantitative analysis of published data. The sample included publications in which the marker was associated with a real therapeutic effect and a clinically interpreted outcome: major ischemic events, bleeding, achievement of blood pressure control, decrease in systolic pressure, or safety parameters.

The absolute risk difference was calculated as the difference in event frequencies between the standard and personalized strategy, and the approximate NNT was calculated as the inverse of this difference in fractions of a unit.

For systematization, a three-level scale of the marker's readiness for implementation was used: high, moderate and low. A formal meta-analysis was not conducted due to the heterogeneity of designs, populations, and endpoints.

RESULTS AND DISCUSSION

The practical value of personalization is determined not by the number of associations found, but by whether it is possible to change the purpose based on them today. Therefore, the initial step of the analysis is to separate the markers by clinical readiness, rather than by novelty or molecular weight. This picture allows you to immediately see where the personalized approach is already working as a drug selection tool, and where it remains in the research area.

For the first step in the practical interpretation, the markers are summarized, which are really able to change the choice of a drug or the control scheme already in the next clinical cycle.

Table 1 - Practical map of markers for choosing antiplatelet and antihypertensive therapy

Marker	Drug/class	What it means	Practical action of a doctor	Readiness
CYP2C19 - intermediate or poor metabolizer	Clopidogrel	Reduced formation of the active metabolite, high residual risk	Transfer to ticagrelor or prasugrel in the absence of contraindications	High
CYP2C19 - non-LOF profile	Clopidogrel	Preserved response to the drug	Clopidogrel is acceptable as a de-escalation option after ACS/PCI	High
High residual platelet reactivity	Antiplatelet agents after PCI	Suspected insufficient P2Y12 inhibition	Selective use in case of recurrent events or very high risk	Moderate
Plasma renin activity < 0.65 ng/ml/hr	Antihypertensive agents	Volume-dependent option, the best chance of responding to a diuretic	Priority of a thiazide diuretic or enhancement of a natriuretic strategy	Moderate
Low renin and high ARR in resistant hypertension	Antihypertensive agents	Sodium-retarding phenotype	Early addition of spironolactone or amiloride in potassium control	High
A2-A3 Albuminuria	ACEi/ARB	A sign of a renal vascular lesion and an indication for a nephroprotective strategy	Reliance on an ACE inhibitor or ARB as the basis of therapy	High

eGFR and potassium	ACEi/ARB, MRA	A marker of the acceptability and safety of treatment	Start, titration and control 2-4 weeks after dose change	High
ADRB1, CYP2D6, GRK5, NEDD4L, multi-gene panels	Beta blockers, thiazides	There are separate associations, but few unified algorithms.	Spot or exploratory application	Low

Table 1 shows the pronounced asymmetry between the two therapeutic areas. In antiplatelet therapy, one test already provides a short route of administration: in the carrier of alleles with reduced CYP2C19 function, clopidogrel becomes less preferable, whereas in hypertension biomarkers of the current pathophysiological condition and safety markers dominate.

This leads to an organizational conclusion: it is better to start implementation not with a wide panel for all cases, but with narrow scenarios with high impact - choosing a P2Y12 inhibitor after PCI, working with resistant hypertension, and routing therapy in patients with albuminuria and chronic kidney disease.

Antiplatelet therapy is an area where personalization has already gone beyond theory. The most convincing pharmacogenetic model in cardiology is related to clopidogrel. The drug is a prodrug and needs to be activated with the participation of CYP2C19 [7]. If the function of the enzyme is reduced, a lower exposure of the active metabolite is formed, platelet inhibition weakens and the likelihood of ischemic complications increases.

From the point of view of practice, not only the escalation of therapy in carriers of an unfavourable genotype works here, but also the reverse course. A patient without alleles of reduced function can keep clopidogrel without automatically switching to a more powerful drug with a higher probability of bleeding. Such a redistribution of therapy is especially interesting for centres where it is necessary to simultaneously reduce ischemic events and avoid unnecessary hyperintension of treatment [9].

To quantify the clinical benefit, the results of key studies in which the genotype guided the choice of an antiplatelet strategy were compared.

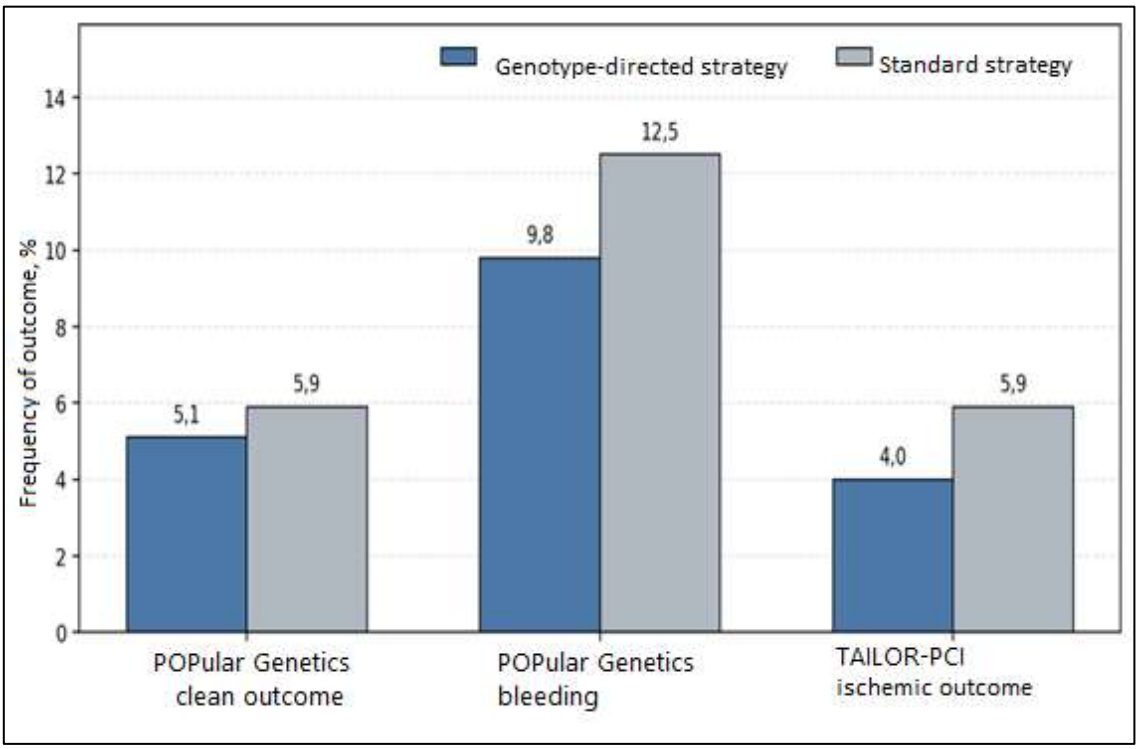

Figure 1 - Comparison of outcomes with genotype-directed and standard antiplatelet therapy, %

Figure 1 shows that the effect of genotyping is unevenly distributed by type of outcome. In the POPular Genetics study, bleeding accounted for the largest gain: 9.8% versus 12.5%. This reflects a clinically understandable mechanism - patients without a genetic limitation were more likely to stay on clopidogrel and less likely to experience bleeding characteristic of more potent P2Y12 inhibitors. The ischemic gain was more modest, but the direction of the differences remained.

In TAILOR-PCI, the picture is slightly different. There, genotyping worked more as a protection of carriers of alleles of reduced function from insufficiently effective clopidogrel. The absolute difference in the primary ischemic endpoint turned out to be moderate, but the clinical significance remains: even a small shift in risk in the population after PCI is important when it comes to stent thrombosis, myocardial infarction and stroke.

In order to convert the percentages into a format convenient for decision-making and pharmacoeconomic assessment, the results of the largest studies are summarized in a table with absolute differences and approximate values of NNT.

Table 2 - Practical interpretation of studies on the genotype-directed choice of antiplatelet therapy

Study	Population	Outcome, %	Absolute benefit	Practical interpretation
POPular Genetics	STEMI, primary PCI, 2,488 patients	Net clinical outcome: 5.1 vs. 5.9	0.8 percentage points; NNT ≈ 125	There is a benefit, but the main contribution to it is the reduction of bleeding.
POPular Genetics	The same population	Major and minor bleeding: 9.8 vs. 12.5	2.7 percentage points; NNT ≈ 37	The best argument in favor of genotyping as a de-escalation tool
TAILOR-PCI	Carriers of CYP2C19 LOF after PCI, 1,849 patients	Ischemic endpoint: 4.0 vs. 5.9	1.9 percentage points; NNT ≈ 53	A potentially clinically significant gain, although the primary p turned out to be borderline
IGNITE real-world	Patients after PCI, 3,342 observations	Alternative therapy reduced the risk of atherothrombotic events in LOF carriers	HR 0.56; relative decrease of about 44.0%	Confirmation of the benefits in real practice without increased bleeding

If we look at the absolute values, the clinical benefit of genotyping is moderate, but quite tangible. To prevent one case of bleeding in the POPular Genetics model, personalized therapy is required in about 37 patients, and the estimated NNT for preventing one ischemic event in LOF carriers in TAILOR-PCI is about 53. For a high-turnover intervention center, this is already a noticeable result.

The test makes the most sense where clopidogrel is actually being considered and a quick switch to ticagrelor or prasugrel is available. Platelet function testing can complement work in selective situations, but it is still inferior to CYP2C19 in terms of reproducibility and clinical clarity [5].

Personalization in hypertension is developing along a different trajectory. If there is one particularly strong gene-drug axis for clopidogrel, then the choice of an antihypertensive agent is more often based on the question of the current mechanism of the disease. Is the volume-dependent component predominant? Is there an activated renin-angiotensin system? Is albuminuria observed as a marker of renal vascular damage? Do kidney function and potassium levels safely enhance the blockade of mineralocorticoid receptors?

Plasma renin activity and the aldosterone/renin ratio attract attention precisely because they link the biology of the disease with the choice of a class of drugs. In the European-American cohorts, a PRA below 0.60-0.65 ng/ml/hr more often corresponded to a volume-dependent phenotype and a better response to a diuretic strategy, whereas at higher values, the probability of a response to RAAS blockade or beta-blocker was higher. In resistant hypertension, low renin and high ARR are particularly well combined with the sodium-retarding variant, where spironolactone shows the most convincing effect [4].

Table 3 summarizes the biomarkers that really help narrow down the choice of a drug class or make it safer.

Table 3 - Biomarkers guiding the choice of antihypertensive therapy

Biomarker	Clinical meaning	Preferred action	Practical limitation
PRA < 0.65 ng/ml/hr	Probable volume-dependent hypertension variant	Thiazide diuretic, strengthening the natriuretic strategy	A better separation is shown in European-American patients; in African Americans, the threshold is less reliable.
PRA ≥ 0.65 ng/ml/hr	A more pronounced renin-dependent component	ACEi, ARB, or beta-blocker for clinical indications	The marker helps guide the choice rather than replace the clinical assessment.
Low renin + high ARR in resistant hypertension	Sodium-retarding phenotype	Spironolactone or amiloride as the most logical enhancement	Supported by the mechanism and results of PATHWAY-2
A2-A3 Albuminuria	Renal vascular lesion requiring nephroprotection	Start or boost ACEi/ARB	Reliance on KDIGO recommendations; especially important in diabetes and CKD
eGFR and potassium	Marker of tolerance and risk of hyperkalemia	Security monitoring at ACEi/ARB and MRA	Creatinine and potassium are assessed 2-4 weeks after starting or titrating

Table 3 shows that in hypertension, personalization is rarely reduced to a single test. The doctor usually faces a sequence of decisions. First, it is determined whether there is an organ lesion requiring a special class of drug, then safety is assessed and, finally, the prevailing hemodynamic or hormonal profile is clarified. That is why albuminuria, eGFR, and potassium are no less important for individualization than conventionally "exotic" markers.

At the same time, you can't hide the limitations. The threshold values of PRA and ARR do not work the same way in different populations, and laboratory techniques require careful standardization. For this reason, biomarkers of the phenotype are better perceived as enhancers of clinical thinking, rather than as an autonomous source of appointment.

Small prospective studies allow us to assess how noticeable the benefits of reducing blood pressure can be with marker-directed regime selection.

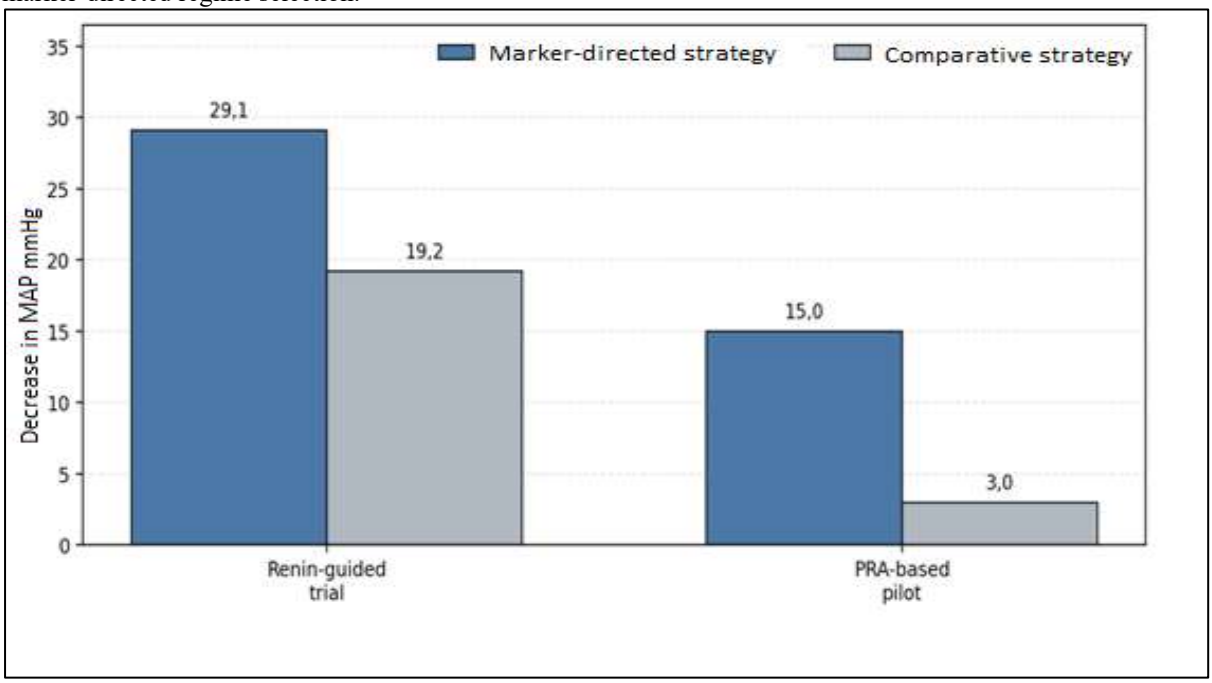

Figure 2 - Reduction of systolic blood pressure with biomarker-directed therapy selection, mmHg

The difference in systolic pressure reduction is impressive: in Renin Test-Guided Therapy, it was 29.1 versus 19.2 mmHg, and in the pilot work with the PRA-based app, it was 15.0 versus 3.0 mmHg. The sample size was small, so it is more reasonable to use these data for difficult-to-control hypertension and multicomponent schemes, and not for mass screening at the first visit.

The most convincing quantitative argument in favor of phenotype-directed selection in hypertension is provided by the PATHWAY-2 study, which compared the options for enhancing therapy in the resistant course of the disease.

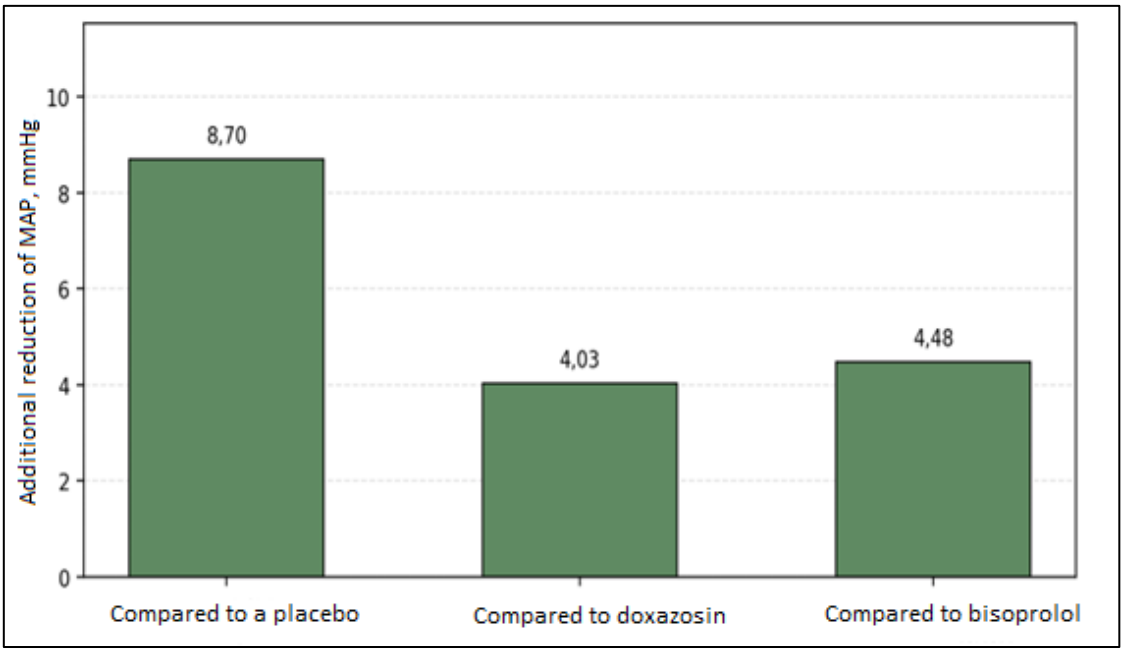

Figure 3 - Additional reduction in home SBP when using spironolactone in PATHWAY-2, mmHg.

Spironolactone confidently outperformed placebo and both active comparators. This is not only a statistical fact, but also a mechanistic clue: resistant hypertension in a significant number of patients is indeed associated with a sodium-retaining phenotype, which is particularly responsive to mineralocorticoid receptor blockade. Here, the biomarker and pharmacology converge very closely.

But the gain in efficacy does not negate the issue of safety. In PATHWAY-2, episodes of potassium elevation above 6.0 mmol/L were rare, but they did occur. Therefore, personalization in this area does not boil down to choosing "spironolactone is better," but rather involves mandatory monitoring of creatinine and potassium levels 2-4 weeks after starting or increasing the dose.

This raises a logical question: if biomarkers are so useful in hypertension, why hasn't pharmacogenetics reached the same level as antiplatelet therapy? The reason is not a lack of biological signals. On the contrary, many associations have been described for beta-blockers, thiazide diuretics, and certain components of RAAS blockade. The issue lies in their inconsistent reproducibility, small effect sizes, and the lack of an algorithm that can reliably transfer findings from one population to another.

The data on beta-blockers and thiazides is particularly revealing. CYP2D6 affects the exposure to metoprolol and the strength of the chronotropic response, ADRB1 and GRK5 can modify the sensitivity to beta-blockade, and NEDD4L is associated with the response to hydrochlorothiazide and the renal handling of sodium. However, the direct translation of these findings into universal prescription rules is still slow [12].

For clarity, the most discussed pharmacogenetic signals of antihypertensive therapy are summarized in Table 4.

Table 4 - Pharmacogenetic markers of antihypertensive drugs and reasons for limited implementation

Gene/ marker	Drug	Observed signal	What hinders implementation	Status
CYP2D6	Metoprolol	Higher exposure and lower heart rate at lower doses	The effect on hard clinical outcomes and tolerability is inconsistent.	Not recommended for routine use
ADRB1	Beta blockers	Receptor variants can change the strength of the response based on heart rate and blood pressure	The effect size is small, and the results are heterogeneous	Promising, without a standard
GRK5	Beta blockers	Modification of sensitivity to beta-blockade	Ethnic specificity and a lack of prospective validation	Niche research
NEDD4L rs4149601	Hydrochlorothiazide	In European patients, the G allele was associated with a more pronounced decrease in blood pressure.	Weak replication in other populations	Candidate, not routine
Combined HCTZ score (PRKAG2, DCC, EPHX2)	Hydrochlorothiazide	It explains about 11.3-11.9% of the response variability	Lack of external broad validation and standardization	Research Panel
ACE, AGTR1, ADD1 and other candidates	RAAS blockers, diuretics	Biologically plausible but unstable associations	There is no single reproducible rule for choosing a drug	The routine is not formed.

Table 4 shows the difference between a 'signal' and a 'destination route'. CYP2D6 affects the concentration of metoprolol, and NEDD4L affects the likelihood of response to thiazide, but a doctor needs more than just an association; they need a testable rule for selecting drugs and doses for different populations. Until such a rule is available, broad pharmacogenetic panels for hypertension risk providing more interpretational noise than benefit. When the results are combined, it becomes clear that the issue is not the possibility of personalized therapy itself, but rather the choice of starting points. Three scenarios look the most convenient for implementation: the choice of P2Y12 inhibitor after ACS/PCI, the management of hypertension in patients with albuminuria and chronic kidney disease, as well as working with resistant hypertension and suspected low-renin sodium-retaining phenotype.

Restrictions are distributed on three levels. Analytical level is associated with the test turnaround time and the reproducibility of the laboratory technique. Clinical - with contraindications, risk of bleeding, kidney function and the probability of hyperkalemia. Organizational - with the cost of the study, the inclusion of the result in the electronic medical record, and the doctor's willingness to interpret it as a basis for action rather than as background information. For hypertension, there is also a population limitation: some of the PRA thresholds and candidate genetic signals are not evenly distributed between ethnic groups.

CONCLUSION

So, to sum up, it is necessary to state the following.

The most mature pharmacogenetic scenario in cardiology is associated with CYP2C19 and clopidogrel; in carriers of reduced function alleles, the choice of ticagrelor or prasugrel has a direct clinical justification.

The absolute benefit of genotyping is moderate, but practical: the gain is more noticeable in terms of reducing bleeding when clopidogrel is rationally left in genetically favorable patients and in reducing ischemic events in LOF carriers.

In antihypertensive therapy, real personalization today is more often based on PRA, ARR, albuminuria, eGFR, and potassium than on broad genetic panels.

Pharmacogenetics of beta-blockers and thiazide diuretics retains scientific potential, but routine application is limited by the heterogeneity of results and the lack of unified prescription algorithms.

The optimal implementation model should be step-by-step and rely only on those tests and biomarkers that quickly change the treatment decision and are integrated into the laboratory monitoring and follow-up route.

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