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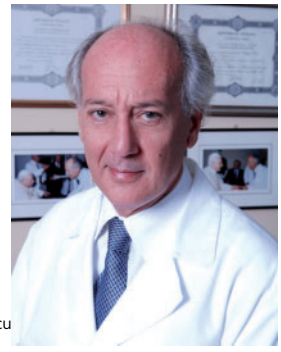
The growing complexity of the number one killer: ischaemic heart disease



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This issue opens with the position paper entitled 'Emergency department management of patients with adult congenital heart disease: a consensus paper from the ESC Working Group on Adult Congenital Heart Disease, the European Society for Emergency Medicine (EUSEM), the European Association for Cardio-Thoracic Surgery (EACTS), and the Association for Acute Cardiovascular Care (ACVC)', authored by Massimo Chessa from the IRCCS Policlinico San Donato in Milan, Italy and colleagues.[1] The authors note that adult congenital heart disease (ACHD) patients represent a growing population with increasing use of acute emergency department (ED) care. Providing comprehensive ED care necessitates an understanding of the most common clinical scenarios to improve morbidity and mortality in this population. The aim of this position document is to provide a consensus regarding the management of the most common clinical scenarios of ACHD patients presenting to the ED.

The issue continues with a focus on ischaemic heart disease. Nearly 200 million people globally suffer from coronary artery disease (CAD), half of whom initially present with chest pain. The optimal non-invasive diagnostic strategy in patients with suspected stable angina is clinically important to define yet remains uncertain. CAD is frequently diagnosed following evaluation of stable chest pain with anatomical or functional testing.[2,3] A more granular understanding of patient phenotypes that benefit from either strategy may enable personalized testing. In a clinical research article entitled '**A phenomapping-derived tool to personalize the selection of anatomical vs. functional testing in evaluating chest pain (ASSIST)**', Evangelos Oikonomou from Yale University School of Medicine in New Haven, CT, USA and colleagues looked in further detail into this matter.[4] Using participant-level data from 9572 patients undergoing anatomical (n = 4734) vs. functional (n = 4838) testing in the PROMISE trial, the authors created a topological representation of the study population based on 57 pre-randomization variables. Within each patient's 5% topological neighbourhood, Cox regression models provided individual patient-centred hazard ratios for major adverse cardiovascular events and revealed marked heterogeneity across the phenomap, suggestive of distinct phenotypic neighbourhoods favouring anatomical or functional testing. Based on this risk phenomap, the authors employed an extreme gradient-boosting algorithm in 80% of the PROMISE population to predict the personalized benefit of anatomical vs. functional testing using 12 model-derived, routinely collected variables, and created a decision support tool named ASSIST. In both the remaining 20% of the PROMISE population and an external validation set consisting of patients from the SCOT-HEART trial undergoing anatomical-first vs. functional-first assessment, ASSIST's testing strategy recommendation was associated with a significantly lower incidence of each study's primary endpoint , as well as of a harmonized endpoint of all-cause mortality or non-fatal myocardial infarction (MI) (*Figure 1*).

Thus, Oikonomou and colleagues propose a novel phenomapping-derived decision support tool to standardize the selection of anatomical vs. functional imaging in the evaluation of stable chest pain, validated in two large and geographically diverse clinical trial populations. This manuscript is accompanied by a thought-provoking **Editorial** from Pamela Douglas from the Duke University Medical Center in Durham, NC, USA.[5] She notes that at each stage, applying dedicated risk classification tools that can guide management decisions in proper sequence will improve patient care, starting with clinical risk algorithms (pooled cohort equations or equivalent) to assist in preventive treatment decisions, followed by the 2019 European Society of Cardiology pre-test probability for the CAD algorithm, the PROMISE Minimal Risk Tool, to identify symptomatic patients who may not require immediate testing, and the ASSIST model to direct patients needing testing to anatomic vs. functional testing.

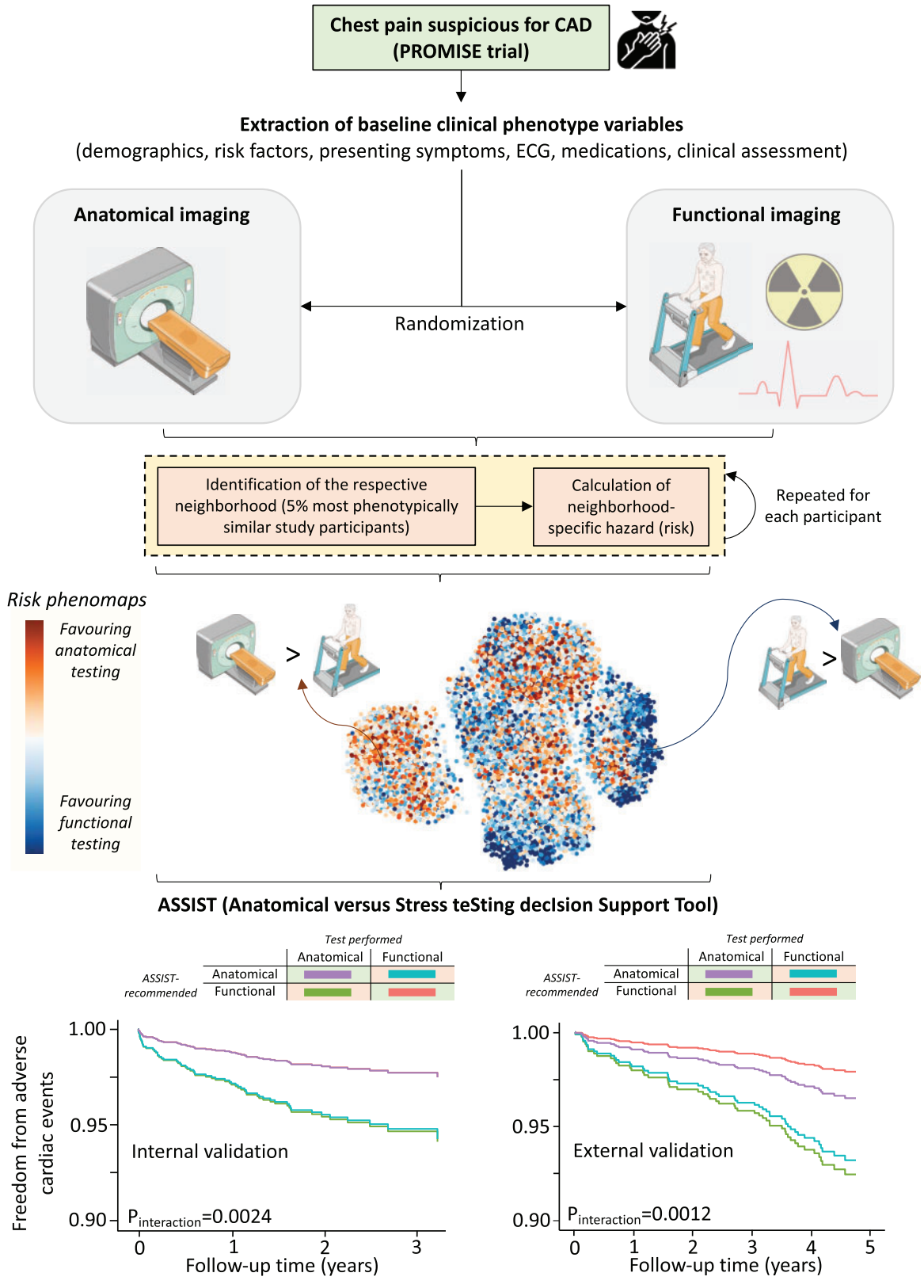

Figure 1 A novel phenomapping approach, trained and validated in patients from two large randomized clinical trials, evaluated the clinical value of coronary computed tomography vs. functional testing to individualize the selection of the appropriate diagnostic test for stable chest pain. See pages 2536–2548.

The Global Registry of Acute Coronary Events (GRACE) score was developed to evaluate risk in patients with MI. The score applies clinical variables, the electrocardiogram, and cardiac biomarkers to estimate risk of future all-cause mortality and MI. The use of the GRACE 2.0 score in patients with non-ST-segment elevation acute coronary syndrome (ACS) is recommended for guiding prognosis across all international guidelines.[6,7] In a clinical research article entitled '**Performance of the GRACE 2.0 score in patients with type 1 and type 2 myocardial infarction**', John Hung from the University of Edinburgh in the UK, and colleagues note that its performance in type 2 MI is uncertain.[8] In two cohorts of consecutive patients presenting to the Emergency Department with suspected ACS from 10 hospitals in Scotland and a tertiary care hospital in Sweden including >60 000 patients, the authors calculated the GRACE 2.0 score to estimate death at 1 year. Discrimination was evaluated by the area under the receiver operator characteristic curve (AUC), and compared for those with an adjudicated diagnosis of type 1 and type 2 MI using DeLong's test. Type 1 MI was diagnosed in 4981 (10%) and 1080 (5%) patients in Scotland and Sweden, respectively. At 1 year, 720 (15%) and 112 (10%) patients died with an AUC for the GRACE 2.0 score of 0.83 and 0.85, respectively. Type 2 MI occurred in 1121 (2%) and 247 (1%) patients in Scotland and Sweden, respectively, with 258 (23%) and 57 (23%) deaths at 1 year. The AUC in type 2 MI was 0.73 and 0.73 for both cohorts, which was lower than for type 1 MI in both cohorts ($P < 0.001$ and $P = 0.008$, respectively).

The authors conclude that the GRACE 2.0 score provides good discrimination for all-cause death at 1 year in patients with type 1 MI, and moderate discrimination for those with type 2 MI. This manuscript is accompanied by an **Editorial** authored by Héctor Bueno from the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in Madrid, Spain, and colleagues.[9] Bueno *et al.* conclude that with the 4th Universal Definition of Myocardial Infarction (4UDMI), we now have better tools for the diagnosis, prognostic assessment, and risk stratification of patients with troponin elevation, suspected ACS, and MI.[10] However, more clinical research is warranted to validate the use of the classification provided by the 4UDMI in unselected patients, to assess its accuracy and reliability, and to evaluate its clinical implications. In addition, given the discordance between the predicted and observed mortality rates at 1 year found in the study by Hung *et al.*, we need to wonder whether the GRACE 2.0 score may need re-calibration.

The use of GLP-1 receptor agonists (RAs) as initial glucose-lowering therapy in type 2 diabetes (T2DM) patients with high risk/established cardiovascular disease (CVD) is controversial since outcome trials on GLP-1 RAs had metformin as background therapy.[11,12] In a clinical research article entitled '**Similar cardiovascular outcomes in patients with diabetes and established or high risk for coronary vascular disease treated with dulaglutide with and without baseline metformin**', Giulia Ferrannini from the Karolinska Institutet in Stockholm, Sweden and colleagues indicate that this post-hoc analysis of the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) trial investigated the effect of dulaglutide on CVD events according to baseline metformin.[13] In REWIND, ~10 000 T2DM patients (31% with established CVD and 69% at high CV risk) were randomized (1:1) to dulaglutide or placebo ion addition to standard of care. The primary outcome was a composite of non-fatal MI, non-fatal stroke, and CVD/unknown death. Key secondary outcomes were microvascular composite endpoint, all-cause death, and heart failure. The effect of dulaglutide in patients with (MET) or without (NOMET) baseline metformin was evaluated by a Cox regression hazard model further adjusted for factors differing at baseline between MET and NOMET, identified using backward selection. Compared with MET (81% of patients), NOMET (19%) were older, leaner, and more often females, with prior CVD events, heart failure, and renal disease. The effect of dulaglutide on the primary outcome did not differ in these two groups (interaction $P = 0.18$). Findings for key secondary outcomes were similar.

The authors conclude that their analysis suggests that the cardioprotective effect of dulaglutide is unaffected by the baseline use of metformin therapy. The manuscript is accompanied by an **Editorial** by Naveed Sattar from the University of Glasgow in the UK and Darren McGuire from the University of Texas Southwestern Medical Center in Dallas, TX, USA.[14] The authors point out that with all new medicines, higher costs are in play and so formal cost-effectiveness analyses would help determine levels of CV risk beyond which such drugs should be recommended. This latter point is far from trivial and was the key difference between ESC and ADA/EASD T2DM treatment algorithms, with the former being far more liberal in its recommending expansion of the use of GLP-1RAs and/or sodium–glucose transporter protein 2 inhibitors. Indeed, if the ESC guidelines were to be followed as stated, a substantially higher percentage of patients in high-income countries would be commenced on such medications, leading to large hikes in drug expenditure. What is not known, however, is to what extent such extra costs would be offset by better disease outcomes. Thus, if further trials challenge metformin's primacy in wider groups of patients, it will lead to profound changes in T2DM therapeutic algorithms.

The improvement in survival of operated patients with congenital heart disease (CHD) has led to an increasing number of adult patients with CHD (ACHD), in particular those with more complex disease. There is general agreement that ACHD patients have special needs.[15] In a clinical research article entitled '**Long-term outcomes after myocardial infarction in middle-aged and older patients with congenital heart disease: a nationwide study**', Maria Fedchenko from the University of Gothenburg in Sweden, and colleagues sought to describe the risk of MI in middle-aged and older patients with ACHD, and to evaluate the long-term outcomes after index MI in patients with ACHD compared with controls.[16] A search of the Swedish National Patient Register identified 17 189 patients with ACHD (52% male) and 180 131 age- and sex-matched controls randomly selected from the general population who were born from 1930 to 1970 and were alive at 40 years of age, all followed up until December 2017 (mean follow-up 23 years). Patients with ACHD had a 1.6-fold higher risk of MI compared with controls ($P < 0.001$), and the cumulative incidence of MI by 65 years of age was 7.4% in patients with ACHD vs. 4.4% in controls. Patients with ACHD had a 1.4-fold increased risk of experiencing a composite event after the index MI compared with controls ($P < 0.001$), driven largely by the occurrence of new-onset heart failure in 42% of patients with ACHD vs. 29% of controls.

The authors conclude that recognizing and managing the modifiable cardiovascular risk factors should be of importance to reduce morbidity and mortality in patients with ACHD. The manuscript is

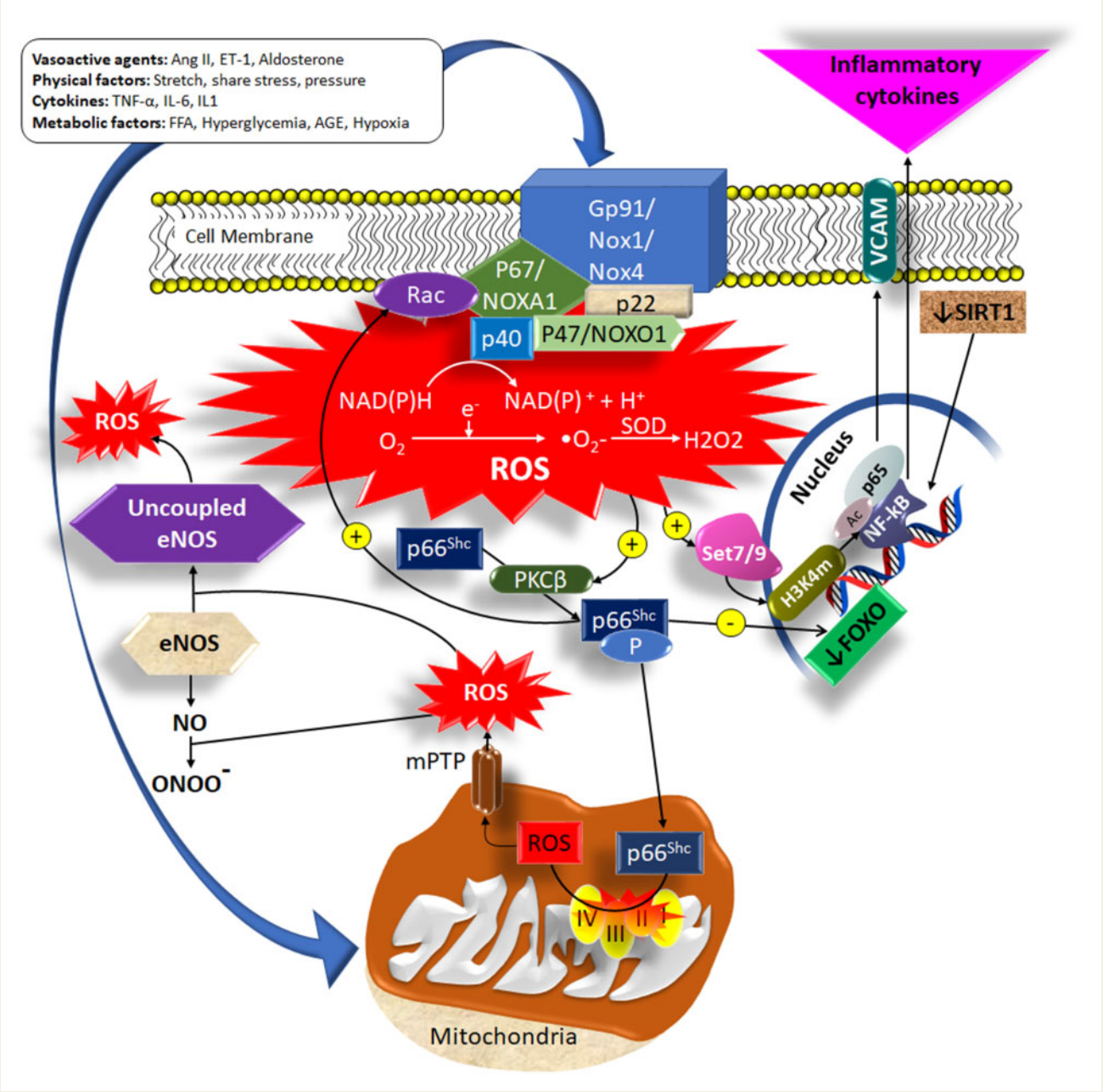

Figure 2 Major pathways leading to ROS-mediated microvascular dysfunction. See pages 2590–2604.

accompanied by an **Editorial** by Gerhard-Paul Diller and Stefan Orwat from the University Hospital Muenster in Germany.[17] The authors conclude that significant advances in the treatment of young patients with congenital heart defects have enabled many to survive into old age. However, it is important to emphasize the fact that these patients also have an increased CV risk, which is determined not only by the classic risk factors, but also by little known, specific ACHD factors. Nevertheless, risk modification and a healthy lifestyle including appropriate weight and nutrition as well as physical exercise must be recommended to all ACHD patients to avoid the detrimental impact on the CV system, particularly on the background of CHD, as highlighted by the current study.

A State of the Art Review entitled '**Assessment and pathophysiology of microvascular disease: recent progress and clinical implications**' by Stefano Masi from the University of Pisa in Italy, and colleagues, also appears in this issue.[18] The development of novel, non-invasive techniques and standardization of protocols to assess microvascular dysfunction has elucidated the key role of microvascular changes in the evolution of cardiovascular damage, and their capacity to predict an increased risk of adverse events.[19,20] These technical advances parallel the development of novel biological assays that enabled the *ex vivo* identification of pathways promoting microvascular dysfunction, providing novel potential treatment targets for preventing cerebral–cardiovascular disease. In this review,

the authors provide an update of diagnostic testing strategies to detect and characterize microvascular dysfunction and suggestions on how to standardize and maximize the information obtained from each microvascular assay. They examine emerging data highlighting the significance of microvascular dysfunction in the development of cardiovascular disease manifestations. Finally, Masi and colleagues summarize the pathophysiology of microvascular dysfunction, emphasizing the role of oxidative stress and its regulation by epigenetic mechanisms which might represent potential targets for novel interventions beyond conventional approaches, representing a new frontier in cardiovascular disease reduction (*Figure 2*).

The issue is further complemented by Discussion Forum contributions related to the '**2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation**'.[6] In a contribution entitled '**Lesson learnt from the new 2020 ESC guidelines on NSTE-ACS: when clinical judgement precedes and overpasses weak recommendations**', Giuseppe Damiano Sanna from the Sassari University Hospital stresses the importance of critically interpreting the Guidelines.[21] In a contribution entitled '**Prasugrel over ticagrelor in non-ST-elevation acute coronary syndromes: is it justified?**' Chia Siang Kow from the International Medical University in Kuala Lumpur, Malaysia and colleagues point out that they believe that ticagrelor should not be discarded as one of the antiplatelet options for patients with ACS presenting without persistent ST-segment elevation in whom a decision is made to proceed with percutaneous coronary intervention.[22] Professor Holger Thiele from the University of Leipzig in Germany and Professor Jean-Philippe Collet from the Sorbonne Université in Paris, France, who chaired the Guideline Committee, respond in two separate comments.[23,24]

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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