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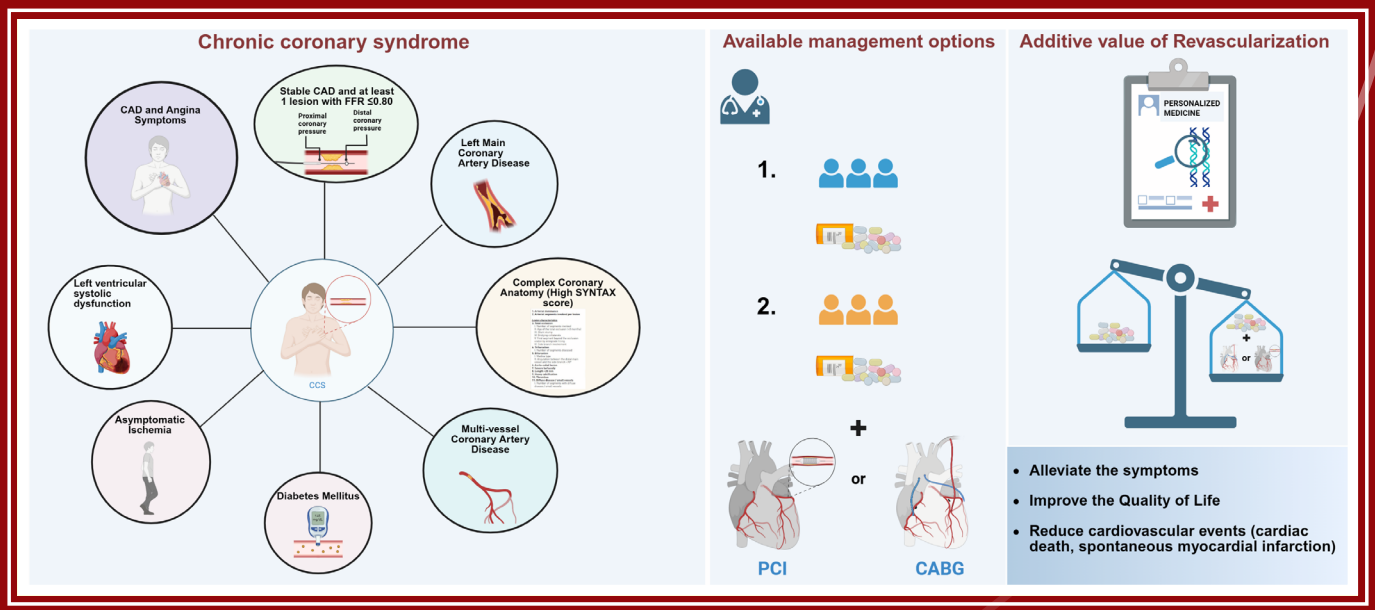

Management of patients with chronic coronary syndrome and the incremental value of revascularization

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CONTENTS

Dear colleagues,

In the current issue, the editorial by Benou et al. highlights recent advances and current evidence in the prevention, diagnosis, and management of congenital cytomegalovirus infection, with emphasis on strategies that reduce long-term sequelae such as hearing loss and neurodevelopmental impairment. The editorial by Miruzzi et al. reviews and discusses the growing evidence supporting a non-biopsy diagnostic pathway for coeliac disease in selected adults, while defining the clinical contexts in which histological confirmation remains necessary.

The original research article by Bakola et al. investigates potential associations between general practitioners' personality traits and the distribution of chronic disease profiles among their patients.

Lastly, the current issue features three review articles. The first, authored by Papageorgopoulou et al., provides an overview of the principles, advantages, and current clinical applications of digital PCR, with an emphasis on its role in diagnostics, therapeutic monitoring, and personalized medicine. The review by Taprantzi D. provides a literature-based diagnostic guide to paraneoplastic syndromes across organ systems, facilitating early recognition of underlying malignancies and improving clinical decision-making. Finally, the review by Papafaklis et al. outlines the current evidence on the role of coronary revascularization, particularly percutaneous coronary intervention, on top of optimal medical therapy in patients with chronic coronary syndrome, focusing on symptom relief, quality of life, and clinical outcomes.

Yours sincerely,

C. Triantos
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and Gastroenterology Faculty of Medicine,
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Recent advances in the prevention and management of Congenital Cytomegalovirus Infection

Sofia Benou, Despoina Gkentzi

Human cytomegalovirus (CMV) is an enveloped DNA virus that, like other members of the *Herpesviridae* family, establishes lifelong latency following primary infection. Reactivation or reinfection with a different CMV strain sometimes occurs and is referred to as recurrent infection [1]. CMV spreads through close contact with infected body fluids, including saliva and urine, particularly from infants and young children, sexual activity, blood transfusion or organ transplantation, as well as during pregnancy or lactation from mother to fetus or infant. Preschool-aged children are the primary source of infection for women of reproductive age and infection among pregnant women most frequently occurs through close contact with young children. CMV infection is typically asymptomatic or causes mild symptoms in immunocompetent individuals. However, it can lead to severe disease in immunocompromised populations, (including HIV-infected individuals and organ transplant recipients), and fetuses, where it may cause congenital CMV (cCMV) infection with potentially serious complications [1-3].

CMV is the most common cause of congenital infection worldwide, with a global prevalence of 0.64%, and the main non-genetic cause of congenital sensorineural hearing loss and neurodevelopmental abnormalities in developed countries [2-3]. About 10% of infants with cCMV infection present with symptomatic infection at birth [4]. Clinical manifestations include hepatosplenomegaly, jaundice, petechial/purpuric rash, auditory and visual impairment, as well as neurologic abnormalities such as microcephaly [5]. Approximately 40–60% of symptomatic newborns will develop a permanent disability, while 10-15% of newborns will develop long-term sequelae. Long-term effects of cCMV include sensorineural hearing loss (SNHL), cognitive impairment, and/or cerebral palsy [4-5].

cCMV can occur after both maternal primary infection and non-primary maternal infection. In seropositive mothers, reactivation of a latent virus or reinfection with a new CMV strain can also affect the fetus, causing cCMV disease with or without sequelae in the newborn and child [6]. Increasing evidence shows that the risk of symptomatic infection, especially when resulting in hearing loss, is similar after maternal primary or non-primary cytomegalovirus infection [2,7]. The risk of vertical transmission after maternal primary CMV infection increases with advancing pregnancy, but fetal sequelae are more likely when infection occurs in the first trimester [8].

Damage due to cCMV, infection may be prevented at various levels, including maternal awareness to prevent infection in pregnancy, prenatal diagnosis of congenital infection followed by antiviral treatment, and neonatal screening to identify the infected babies who could receive antiviral agents when indicated in order to prevent sequelae [2].

Expert consensus guidelines for cCMV infection diagnosis and management were published in 2017 [9] and revised in 2024 [10]. Of note, both prevention and management of cCMV infection remain the key principles in reducing the disease burden.

Primary prevention of cCMV infection remains the optimal and most effective way to reduce the disease

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burden. Exposure to young children is the main risk factor for maternal primary CMV infection, as infected children excrete the virus in their urine and saliva over a long period. Mothers of children attending daycare and childcare workers are considered high-risk populations [11]. Several studies have suggested that hygiene measures considerably reduce the risk of contracting a maternal primary infection during pregnancy while there is limited evidence about the role of hygiene measures in non-primary maternal infection [10]. However, in the absence of a licensed effective vaccine, the best primary prevention strategy for CMV infection in pregnancy is education on hygiene precautions [2]. The latter should be provided to all pregnant women regardless of their CMV serostatus [10]. Despite the impact of cCMV on newborn and children's health, low awareness has been reported in the literature among both pregnant women and healthcare professionals regarding cCMV infection and their preventive measures [12].

Maternal CMV infection in pregnancy, both primary and non-primary, is commonly asymptomatic making the diagnosis challenging, particularly in the absence of routine antenatal screening. Serological testing can only diagnose maternal primary infection, while it is often unhelpful in non-primary infection. There is no screening test for non-primary infection during pregnancy that will predict the likelihood of congenital infection. The diagnosis and management of CMV infection during pregnancy have therefore focused on primary maternal infection.

CMV serology is essential to identify women at risk of maternal primary infection during pregnancy but also for diagnosing a maternal primary infection. Depending on local epidemiology, universal first-trimester CMV serology should be considered in women with unknown or negative CMV serostatus. CMV serology in the first trimester of pregnancy as early as possible is recommended, followed by a retest every 4 weeks until 14–16 weeks in seronegative women [10]. CMV serology is not recommended in pregnant women beyond 16 weeks except in cases with ultrasound CMV compatible symptoms [10].

The diagnosis of maternal primary infection is based on CMV IgM detection. CMV IgM is present in 50–80% of sera for up to 6 months after maternal primary infection and cross-reactivity as well as non-specific reactivity may occur, resulting in low specificity for diagnosing a recent infection [10]. As a result, IgG avidity testing is used to exclude or confirm a recent (less than 90 days) maternal primary infection in cases with positive IgM and positive IgG. Low avidity indicates recent maternal primary infection. High IgG avidity in the first trimester allows with a high probability to exclude a recent maternal primary infection during the first trimester and the preconceptional (two–eight weeks before conception) period [10]. In any case of primary maternal infection, all efforts must be made to ascertain the timing of infection, since it influences the risk of vertical transmission and the risk of long-term sequelae.

CMV DNA detected by PCR in a sample of amniotic fluid is the gold standard for the diagnosis of fetal infection. An amniocentesis for CMV should be performed when maternal primary infection is revealed by maternal symptoms or following prenatal serology screening or when prenatal ultrasound is suggestive of fetal infection [2]. Amniocentesis can be scheduled after 17 weeks of gestation and at least six–eight weeks after the suspected maternal infection [13]. Perinatal outcome following confirmed fetal cytomegalovirus infection ranges from healthy asymptomatic livebirth to stillbirth or postnatal survival with severe disability [2]. Oral valacyclovir at a dose of 8g/day is recommended following maternal primary infection in early pregnancy, as soon as possible after infection and until the result of the CMV PCR in amniocentesis [10]. In confirmed fetal infection, women should undergo serial targeted fetal ultrasounds in combination with third-trimester magnetic resonance imaging (MRI), to collect complementary prognostic information.

Diagnosis of cCMV infection is based on positive CMV DNA PCR in infant's urine within three weeks of life [2]. Saliva PCR testing may serve as an alternative diagnostic method but requires confirmation with urine testing. Retrospective testing via PCR of dried blood spots, routinely collected in the first week after birth, enables diagnosis in children older than 3 weeks of age [10].

In the neonatal age, cCMV infection might be symptomatic or asymptomatic. Indications for testing for cCMV include evidence of maternal primary infection during pregnancy, presence of indicative features on prenatal ultrasonography or MRI or neonatal clinical manifestations consistent with cCMV [10]. The strongest evidence exists for SNHL either bilateral or unilateral. However, a major challenge for physicians caring for newborns remains early detection of long-term cCMV-complications -particularly SNHL, among infants asymptomatic at birth [4,14]. Indeed, early identification

of SNHL allows timely interventions that will optimize speech outcomes [5]. As a result, despite the implementation of targeted cCMV screening for newborns who fail universal neonatal hearing screening, concerns remain about inadequacy of this approach in properly identifying all infected infants who are at risk of complications [15]. Cost-effectiveness of universal versus targeted cCMV screening remains a major topic of debate among literature [16].

Investigations following virological diagnosis of cCMV infection should access organ involvement to predict outcome and guide treatment decisions. All infected newborns should be evaluated with a clinical examination that includes anthropometrics, full blood count, liver enzymes, bilirubin (total and conjugated), ophthalmologic and audiologic assessment. Regarding the evaluation of the central nervous system, while cranial ultrasound (cUS) is the first-line imaging modality, MRI can reveal significant abnormalities, such as white matter changes and cortical malformations, frequently missed by cUS. Overall, blood viral load tends to be higher in symptomatic infants, though, there is no consensus for a threshold for risk stratification [10,17].

Infants with significant symptoms/signs of cCMV should be treated with antivirals (intravenous ganciclovir at a dose of 6mg/kg/dose, twice daily, or its oral pro-drug valganciclovir at a dose of 16 mg/kg/dose, twice daily) [2]. Antiviral treatment for 6 months is recommended in significant CMV-related symptoms at birth or isolated hearing loss [10,18]. For infants with isolated persistent thrombocytopenia or hepatitis and no other manifestation, antiviral treatment for six weeks is recommended. Oral valganciclovir is the treatment of choice, but intravenous ganciclovir may be used for infants unable to take enteral medication, switching to oral route as soon as possible. Antiviral treatment should be started as early as possible and before the first month of age [10].

During antiviral treatment, full blood count and liver function tests should be checked regularly. Hearing screening follow-up, ophthalmological and neurodevelopmental assessments, and vestibular testing should be performed based on the severity of disease and estimated timing of infection. Hearing follow-up is recommended up to five years of age for infants with normal hearing at birth and unknown timing or first-trimester infection. Asymptomatic children with normal imaging and documented maternal primary infection in the second or third trimester may follow standard pediatric care [10]. In conclusion, cCMV infection constitutes a significant burden on patients, family and society. A multidisciplinary team including psychological support may be very helpful for families in the early stages of the journey.

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Rethinking Coeliac Disease Diagnosis: Is Biopsy Still Necessary?

Lara Miruzzi, Pierre Ellul, Martina Sciberras

Coeliac Disease (CeD) is a chronic autoimmune condition affecting the small bowel that is triggered by an abnormal immunological response to the gliadin component found in gluten. Globally, the prevalence of diagnosed CeD is estimated to be 1% of the population [1]. Currently, the diagnosis of CeD entails a complex process including referral to a gastroenterologist, assessment of patient symptomatology, serology and upper gastrointestinal (GI) endoscopy with biopsies from the second part of the duodenum and the duodenal bulb demonstrating villous atrophy and intraepithelial lymphocytosis (IEL) [2].

In fact, duodenal biopsies obtained through upper GI endoscopy have played a central role for years and are currently considered to be the gold standard for the diagnosis of CeD in adults. However, a gastroscopy is an invasive procedure with potential risks for patients [3]. Moreover, there may be variation in interpretation and grading by histopathologists and the patchy nature of CeD may miss certain cases. There is additional financial costs of the procedure and pathology specimens and a delay in diagnosis may occur due to waiting lists for endoscopy [4].

Paediatric guidelines by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have approved new criteria for a non-biopsy approach to CeD when IgA anti-tissue transglutaminase antibody (anti-TTG IgA) levels are more than 10 times the upper limit of normal (ULN) and anti-endomysial antibodies (EMA) are positive irrespective of value [5].

In adults, scientific literature supporting a non-biopsy approach for the diagnosis of CeD is growing and the implications of adopting such an approach are being debated. A recent systematic review and meta-analysis by Shiha MG et al, which included 18 international studies and more than 12,000 adult patients, concluded that selected adults with anti-TTG IgA ≥10 times the ULN and a moderate to high pre-test probability of CeD (guided by patient symptomatology and risk factors for CeD) can be diagnosed without undergoing invasive endoscopy and duodenal biopsies [6]. Further studies in adult patients found that, in different settings, anti-TTG IgA ≥10 the ULN predicts the presence of mucosal atrophy from 95.2% in low-risk populations to 100% in high-risk populations [7,8,9]. Patients were subclassified into risk categories based on clinical context: high risk included those with a strong clinical suspicion of CeD, moderate risk included first-degree family members of individuals with CeD, and low risk included individuals from the general population. The study by Penny et al, looked at a cohort of patients with high anti-TTG IgA titres, drawn from multiple international centres. Marsh 3 histology was used as the reference standard for determining CeD. The performance of anti-TTG IgA ≥10 the ULN was assessed against this benchmark, demonstrating a positive predictive value (PPV) of 95.2% in diagnosing CeD [8]. Supporting this, a Scottish study by Hoyle et al, reported that the majority of patients with TTG-IgA >10× ULN were confirmed to have CeD, with an even higher PPV of 99.58% [9]. A study by Baykan AR et al, postulates that a higher anti-TTG IgA correlates with more damage to the mucosa noted on histology with a higher score on the Marsh classification [10].

Anti-TTG IgA has been shown to have a strong PPV in the diagnosis of CeD. A prospective multicenter, international study provided further evidence for a non-biopsy approach as it confirmed that both a 5-fold and

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a 10-fold increase of TTG in a high-risk population were able to predict mucosal atrophy in 97.4% and 97.5%, respectively, when the biopsy was interpreted locally. The histology was then reviewed by the central expert pathologist and it was noted that the PPV of a 10-fold elevation in TTG was 99.4% [11]. This indicates that the discrepancy was mainly due to misinterpretation of the histology. The only case in this study with a 10-fold rise in TTG that did not show histological evidence of atrophy had an increased IEL and crypt hypertrophy. This patient was eventually diagnosed with CeD on the basis of a very high serological titer, symptomatology, and improvement reported by the patient after adopting a gluten-free diet (GFD) [12]. The results of a retrospective study by Cauchi S et al, also align with these findings. This latter study also showed that all patients with an anti-TTG IgA ≥10 the ULN had a positive EMA result and none of those with a negative result were diagnosed with CeD [13]. This supports the statement in the ESPGHAN guidelines that testing for EMA serology increases the accuracy of a non-biopsy approach [5].

During the COVID-19 pandemic the non-biopsy approach was implemented by the British Society of Gastroenterology guidance in those adult patients with an anti-TTG IgA ≥10 × ULN and no other alarm symptoms [10]. One prospective and two retrospective studies from the UK evaluating whether the non-biopsy approach in adults with an anti-TTG IgA ≥10×ULN was feasible, showed that no other concurrent pathology was found, and confirmed histological diagnosis of CeD was reported in >95% cases across all three studies [8,14,15].

A Finnish multicentre retrospective study by Ylönen V et al, compared the performance of four commercial anti-TTG IgA assays [16]. Serology samples from 836 Finnish adults with either a family history of CeD or suspected CeD were analysed. From the total cohort, 137 patients with suspected CeD and 85 patients with family history of CeD had histologically confirmed CeD. The PPV for a 10 × ULN threshold was 100% across all anti-TTG IgA assays [1]. Therefore, the serological diagnosis of CeD in adults using different commercial kits and applying the criterion of a value more than 10 × ULN was accurate. In addition, the study also suggested that a lower ULN threshold could be appropriate in the non-biopsy approach but that more research is needed [15].

Despite the above, applying the non-biopsy approach for the diagnosis of CeD is not as straightforward in adults as in pediatrics. There are several circumstances where a gastroscopy should still be performed, especially when patients present with 'red flag' symptoms. These include weight loss, iron deficiency anemia, dysphagia and persistent dyspepsia among others [8]. Some of these symptoms and signs are also common in CeD, underscoring the importance of referring patients to a gastroenterologist before establishing a diagnosis. Furthermore, biopsies should be considered where the serology results and clinical risk are not concordant or in cases with a borderline serology result. In addition, patients having persistent symptoms despite adherence to a GFD will require duodenal biopsies, as anti-TTG IgA is not a reliable marker of histological improvement [8].

Moreover, biopsies may be required when there is suspicion of CeD-related complications, including ulcerative jejunitis and small-bowel T cell lymphoma. Several risk factors have been identified for the development of such complications, including persistent diarrhoea, older age at diagnosis, having seronegative CeD as well as being homozygous for the HLA-DQ2.5 haplotype. These factors should be taken into consideration when considering a non-biopsy approach in the future [12,17].

The implementation of the non-biopsy approach requires a high level of anti-TTG IgA in order to avoid uncertain diagnoses or the misinterpretation of serological results especially by other medical professionals. A borderline increase in the serology may indicate a false positive result, the patient could have taken the test whilst already on a GFD or may have IgA deficiency thus creating a spurious result [12]. Another key issue is long-term adherence whereby patients who receive a biopsy-confirmed diagnosis may be more likely to adhere to a strict GFD compared to those diagnosed based solely on serology. This may be due to the perceived certainty of a histological diagnosis as compared solely to a serological diagnosis.

The non-biopsy approach to diagnosing CeD represents a step toward less invasive and more efficient diagnostic pathways. This strategy holds particular promise in lower-income countries or regions with limited access to timely gastroenterology services, where endoscopic resources may be scarce. While this method can reduce patient burden and healthcare costs, clinicians must carefully evaluate individual cases, balancing the benefits of avoiding unnecessary procedures with the need for diagnostic accuracy. Cur-

rent evidence supports its use in selected adults with markedly elevated anti-TTG IgA antibody levels; however, further studies are necessary to refine the criteria, validate long-term outcomes, and ensure sustained adherence to a gluten-free diet.

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Do Physician Personality Traits Influence Patient Profiles? A Cross-Sectional Study in Greek Primary Care

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Abstract

Background: The personality traits of physicians may subtly influence the type of patients they attract and the disease categories they manage. Although communication styles and therapeutic approaches have been linked to interpersonal traits, the potential correlation between personality and the epidemiological profile of patients in primary care remains underexplored.

Methods: A cross-sectional exploratory study was conducted using a structured online questionnaire distributed to 82 general practitioners (GPs) in Greece. Data collected included physician demographics, estimated patient counts per disease category and personality profiles based on the IPIP-50 Big Five Inventory. Statistical analysis was performed using Python and Excel tools, including descriptive analysis, Spearman's correlation (selected for robustness to non-normality) and linear regression modeling used in an exploratory manner to assess explanatory power.

Results: Extraversion was significantly associated with a higher number of patients with diabetes ($\rho = 0.29$, $p = 0.005$). Other Big Five traits demonstrated no statistically significant correlation with disease categories. Regression models revealed overall low explanatory power, including for diabetes ($R^2 = 0.196$). Additionally, gender-based differences were observed, with male physicians scoring higher in Emotional Stability and Openness. No significant associations were found between personality traits and physicians' age, experience, or chronic illness history.

Conclusions: Physician personality traits, particularly extraversion, may be weakly associated with the type of chronic patients encountered, especially in conditions requiring frequent interaction and adherence strategies such as diabetes. However, organizational, demographic, and health system–level factors are likely to exert stronger influences on patient distribution. This study highlights the need for further exploration using larger samples, objective patient records, and longitudinal or mixed-method designs to better understand the interplay between physician psychology and patient behavior in primary care contexts.

Key words: *Physician personality; Big Five traits; primary care; chronic disease; diabetes*

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INTRODUCTION

The physician–patient relationship is a cornerstone of effective clinical practice, particularly in primary care settings where longitudinal engagement and trust are critical. While clinical competence and systemic struc-

tures are key determinants of care quality, a growing body of evidence suggests that physicians' personality traits also influence various aspects of medical interaction, including communication patterns, empathy, stress response, and even diagnostic behavior [1,2]. These interpersonal dimensions may be especially salient in primary care, where sustained contact and continuity of care shape both clinical outcomes and patient retention.

The Five-Factor Model (also known as the Big Five) has become a widely accepted taxonomy in personality psychology, encompassing the dimensions of Extraversion, Agreeableness, Conscientiousness, Emotional Stability (the inverse of Neuroticism), and Openness to Experience [3]. These traits have been associated with professional behavior and well-being among healthcare professionals [4], as well as with clinical decision-making under uncertainty, burnout susceptibility, and responsiveness to patient distress [5]. Accordingly, personality traits have been increasingly examined as potential modifiers of clinical practice style rather than direct determinants of clinical competence.

However, despite increasing interest in personality-based studies in medical education and health psychology, limited empirical evidence exists regarding whether a physician's personality influences the types of patients they attract or retain. Particularly in primary care, where physicians often act as a gatekeeper and longitudinal health managers, it is conceivable that the interplay of personality and patient characteristics might generate non-random patterns in patient distribution by diagnosis or disease type. At the same time, such potential effects are likely to be modest and embedded within broader organizational and system-level determinants of care delivery.

This study aims to address this gap by exploring whether specific personality traits of general practitioners (GPs) correlate with the prevalence of chronic diseases among their regular patients. Conducted within the context of the Greek Primary Health Care (PHC) system, the study uses a structured psychometric instrument to assess personality and investigates associations with patient population characteristics. Adopting an exploratory approach, it seeks to determine whether physician personality can be considered a secondary and non-dominant contributing variable in the epidemiological landscape of outpatient care, complementing traditional determinants such as demographics, training and health system design.

MATERIALS AND METHODS

Study Design and Population

This was a cross-sectional, observational exploratory study conducted between April and May 2025. The sample included 82 GPs working in various Primary Health Care Units across Greece. Participants were recruited through targeted email invitations distributed to professional medical associations, PHC networks, and university-affiliated physician groups. Inclusion criteria were active clinical practice in a PHC setting and willingness to provide data through a structured online survey. Given the sample size and recruitment strategy, the study was designed to generate hypotheses rather than to support causal inference or population-level generalization.

Survey Instrument

The research instrument consisted of a three-part structured questionnaire developed in Google Forms:

1. Demographic and professional characteristics: age, sex, geographic region, years of clinical experience, chronic illness status, and employment sector (public/private).
2. Patient disease profiles: physicians were asked to estimate the number of patients they manage regularly in seven chronic disease categories: diabetes (E08-E13), anxiety and stress related disorders (F40-48), depression (F32.9), chronic obstructive pulmonary disease (COPD) (J40-44), osteoarthritis (M15-M19), coronary heart disease (I10-I25), and cerebrovascular disease, stroke (I63).
3. Personality traits: assessed via the IPIP-50 inventory, a publicly available and psychometrically validated tool that measures the Big Five personality traits using a five-point Likert scale [6].

The questionnaire underwent face validation by a panel of three experts in psychology and primary care medicine before dissemination. Average completion time was approximately 10–12 minutes.

Data Collection and Ethics

All responses were collected anonymously. Participants provided informed consent electronically, and the study protocol was reviewed and approved by the Research Ethics Committee (REC) of the University

of Patras, Greece (**15926/19-12-2023**). No patient-identifiable data were used or collected.

Data Processing

Data were exported to Microsoft Excel for initial cleaning and subsequently processed in Python 3.10 using the Pandas, NumPy, and SciPy libraries. Outlier control was performed by visual inspection, and biologically implausible extreme values (e.g., unrealistically high patient counts) were replaced with the median value of the respective variable to reduce distortion of the results, rather than excluding entire observations. Given the self-reported nature of caseload estimates, no imputation was applied, and descriptive statistics were computed for all variables using complete-case data only.

Statistical Analysis

Spearman's rank correlation coefficient was used to explore monotonic associations between personality traits and the number of patients in each disease category, as this method is robust to non-normal data distributions and appropriate for exploratory analyses in relatively small samples [7]. Independent samples t-tests were used to examine personality differences by gender, chronic illness status, and employment sector. Where distributional assumptions were not fully met, results were interpreted conservatively. Multiple linear regression models were constructed to evaluate the exploratory explanatory capacity of each Big Five trait on disease-specific patient counts, using one trait per model to avoid multicollinearity and to reduce instability in coefficient estimation. Statistical significance was set at $p < 0.05$, with emphasis placed on effect size magnitude and overall model performance rather than statistical significance alone. No imputation was applied, and all analyses were based on complete-case data to preserve transparency given the self-reported nature of the dataset.

All visualizations and statistical outputs were generated in Python using the Matplotlib and Seaborn libraries. Figures were designed to facilitate descriptive interpretation rather than inferential generalization. Summary statistics and plots are presented in Figures 1 and 2.

RESULTS

Sample Characteristics

A total of 82 GPs completed the survey. The majority were female (n = 54, 67.1%) and worked in the public sector (90.2%). Most respondents were aged 40–60 years, with a mean age of 49.6 years (SD = 8.2) and an average of 13.9 years of professional experience in primary health care. Approximately 34.1% reported a personal history of chronic illness. No statistically significant associations were observed between demographic variables (age, years of experience, chronic illness status) and personality trait scores. Descriptive statistics of participant demographics are presented in Table 1.

Patient Profiles

Respondents estimated the number of patients they regularly manage in seven predefined chronic disease categories (Figure 1). The most frequently encountered condition was diabetes mellitus, followed by osteoarthritis and coronary heart disease. Psychosomatic conditions such as anxiety-related disorders and depression were less prevalent in the reported patient mix. Variation in patient distribution was observed across physicians but showed no systematic association with demographic variables. It should be noted that certain conditions, such as COPD, may be partially managed in specialist settings, potentially contributing to lower representation in GP-reported caseloads. Outlier control procedures were applied through visual inspection, and biologically implausible extreme values were replaced with the median value of the corresponding variable to minimize distortion of descriptive and inferential statistics, without excluding entire observations from the analysis.

Personality Trait Scores

Personality assessment via the IPIP-50 inventory yielded the mean trait scores (on a 1–5 Likert scale) presented in Table 2. Trait scores were approximately normally distributed (Figure 2). Male physicians scored significantly higher than female physicians in Emotional Stability ($p = 0.001$) and Openness to Experience ($p =$

Table 1. *Characteristics of the study population (n=82).*

	n	%	95% CI (%)
Female	54	67.1	56.3–76.3
Public sector employment	74	90.2	81.9–95.0
Chronic illness (self-reported)	28	34.1	24.8–44.9

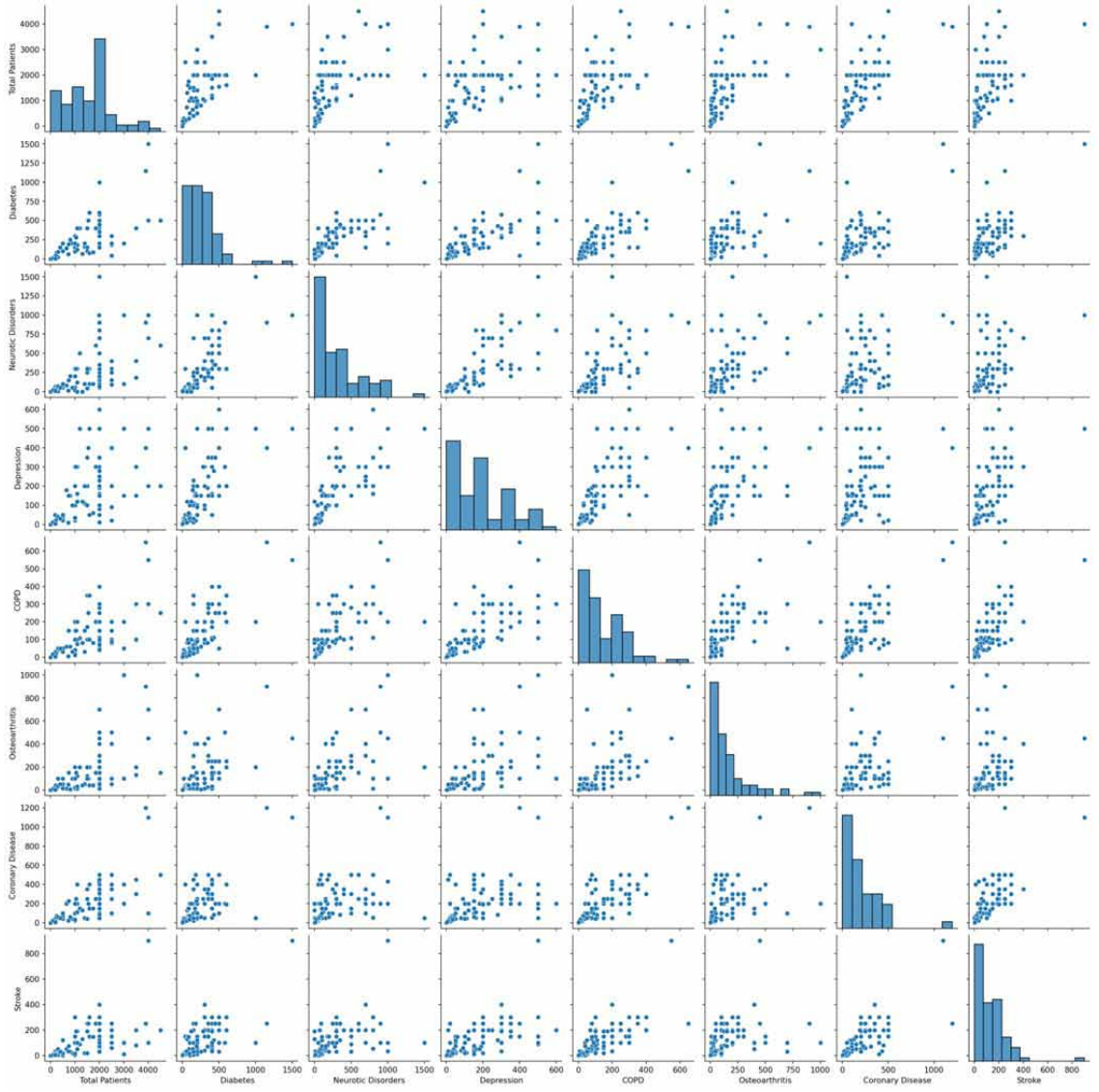

Figure 1. Analysis of Patient Profiles Managed by Physicians.

Figure 1 presents a pairwise scatterplot matrix (with histograms on the diagonal) illustrating the distribution and interrelationships among the numbers of patients managed by participating physicians across multiple chronic disease categories. Each row and column corresponds to a specific patient group, including total patients, diabetes, anxiety-related disorders, depression, COPD, osteoarthritis, coronary heart disease, and stroke. Diagonal panels (histograms) show the univariate distribution of patient counts for each condition. These distributions are generally right-skewed, indicating that most physicians manage relatively small to moderate numbers of patients per condition, while a smaller number report substantially higher caseloads. Off-diagonal panels (scatterplots) display bivariate relationships between pairs of disease categories. Each point represents one physician, plotted according to the number of patients managed in the two corresponding categories. The scatterplots reveal considerable variability across physicians, with no strong linear patterns for most disease combinations. Overall, the figure highlights the heterogeneous nature of GP caseloads and supports the conclusion that patient distributions vary substantially between physicians, without clear clustering or strong interdependence across most chronic disease categories.

0.027) (Figure 3). No statistically significant differences were observed based on chronic illness status or employment sector. The observed gender differences were not associated with systematic variation in patient disease profiles.

Correlation Analysis

Spearman's rank correlation coefficients were calculated to assess relationships between personality traits and the number of patients managed per disease category. A statistically significant positive correlation was observed

Table 2. *Personality trait scores.*

	Mean score	Standard Deviation
Extraversion	3.05	0.68
Agreeableness	4.01	0.73
Conscientiousness	3.80	0.52
Emotional Stability	3.10	0.71
Openness to Experience	3.62	0.5

between Extraversion and the number of patients with diabetes ($\rho = 0.29$, $p = 0.005$) indicating a weak-to-moderate association. No other significant correlations were found across the remaining traits and conditions (Figure 4).

Regression Models

Seven multiple linear regression models were constructed, each using one Big Five trait as an independent variable and the number of patients per disease category as the dependent variable. Only the model examining Extraversion and diabetes demonstrated a positive coefficient with explanatory value ($R^2 = 0.196$). Even in this case, the proportion of explained variance was limited and all other models yielded negligible or negative R^2 values, underscoring the absence of meaningful predictive capacity of personality traits for patient caseload composition (Figure 4).

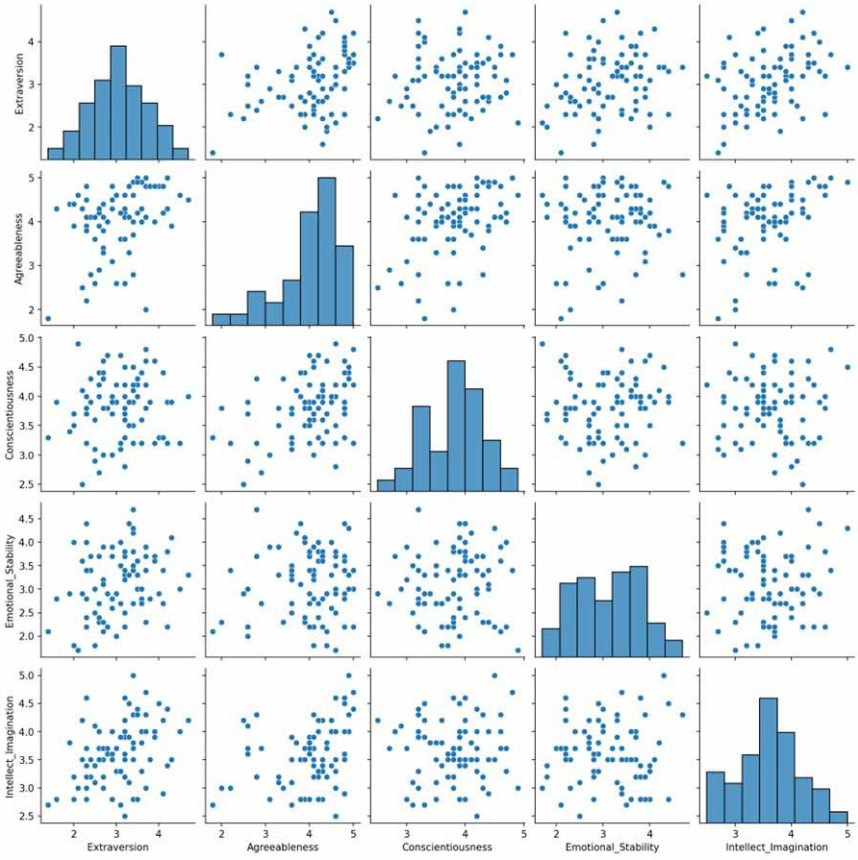

Figure 2. Analysis of Physicians' Personality Trait Scores.

Figure 2 presents a pairwise scatterplot matrix with histograms on the diagonal illustrating the distribution and interrelationships among the five personality traits of participating physicians, as measured by the IPIP-50 Big Five inventory: Extraversion, Agreeableness, Conscientiousness, Emotional Stability, and Intellect/Imagination (Openness to Experience). Diagonal panels (histograms) depict the univariate distribution of each personality trait. All traits show approximately normal to mildly skewed distributions, centered around mid-to-high values on the 1–5 Likert scale. This indicates relatively balanced personality profiles within the sample, with no extreme clustering at the scale boundaries. Off-diagonal panels (scatterplots) display the bivariate relationships between pairs of personality traits. Each point represents an individual physician. The scatterplots reveal weak to moderate positive associations between some traits (e.g., Agreeableness and Conscientiousness), while most trait combinations show substantial dispersion and no strong linear patterns. Overall, the absence of tight clustering or pronounced linear trends suggests that the Big Five dimensions in this physician sample are largely independent, consistent with the theoretical structure of the Five-Factor Model.

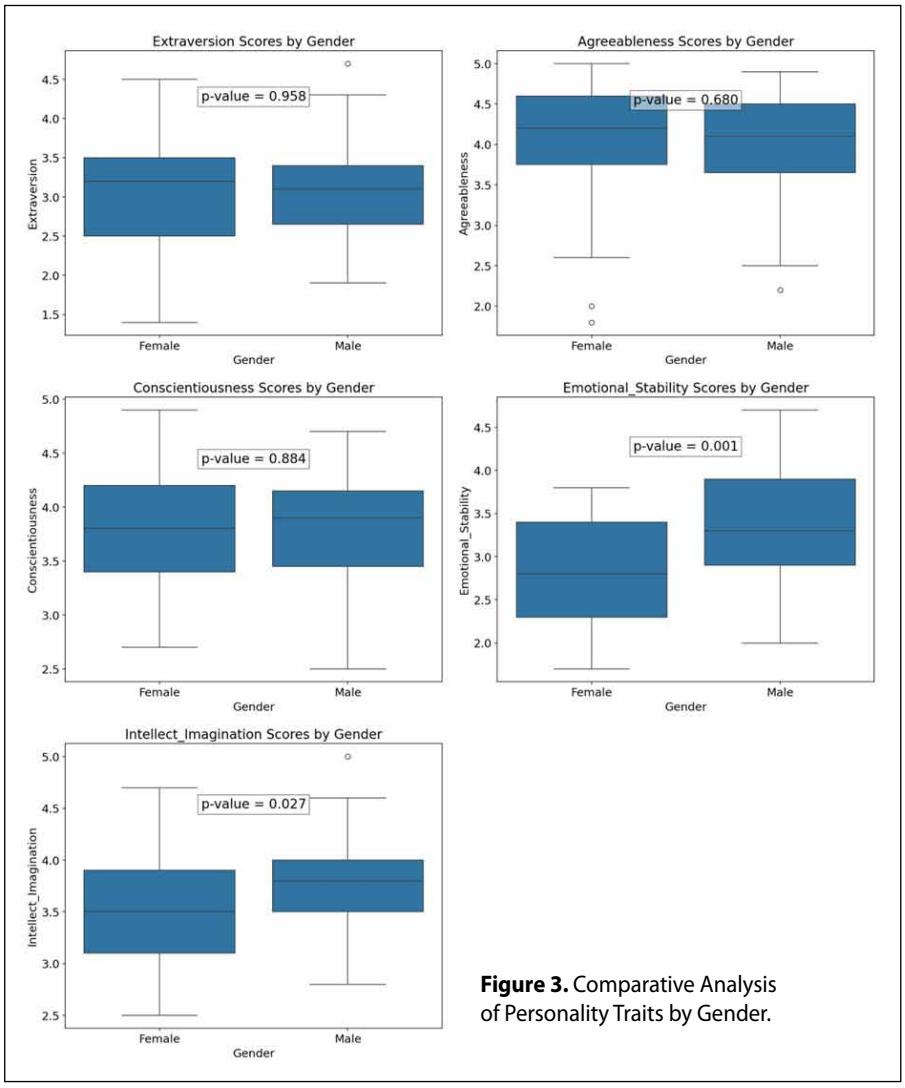

Figure 3. Comparative Analysis of Personality Traits by Gender.

DISCUSSION

This study examined whether the personality traits of GPs influence the profiles of patients they manage in primary care, particularly across chronic disease categories. The findings suggest that while Extraversion may be positively associated with the number of patients with diabetes, this association is weak and does not translate into meaningful predictive capacity, and no significant correlations emerged for other personality traits or disease groups. Furthermore, male physicians scored higher than female physicians in Emotional Stability and Openness to Experience, results consistent with certain findings in the medical psychology literature [8] but not associated with systematic differences in patient disease profiles.

The observed association between Extraversion and diabetes may be attributable to the interpersonal demands of diabetes management, which often requires frequent physician–patient interaction, counseling, and behavioral support. Extraverted physicians are more likely to engage actively with patients, employ collaborative communication styles, and foster ongoing therapeutic relationships, factors that can enhance patient retention and trust [9,10]. Consequently, diabetic patients, who frequently require long-term follow-up and lifestyle modification, may gravitate toward or remain longer with physicians exhibiting these traits. Nevertheless, the low proportion of explained variance indicates that such interpersonal mechanisms operate alongside, rather than independently of, broader structural determinants of care.

Contrary to expectations, no significant associations

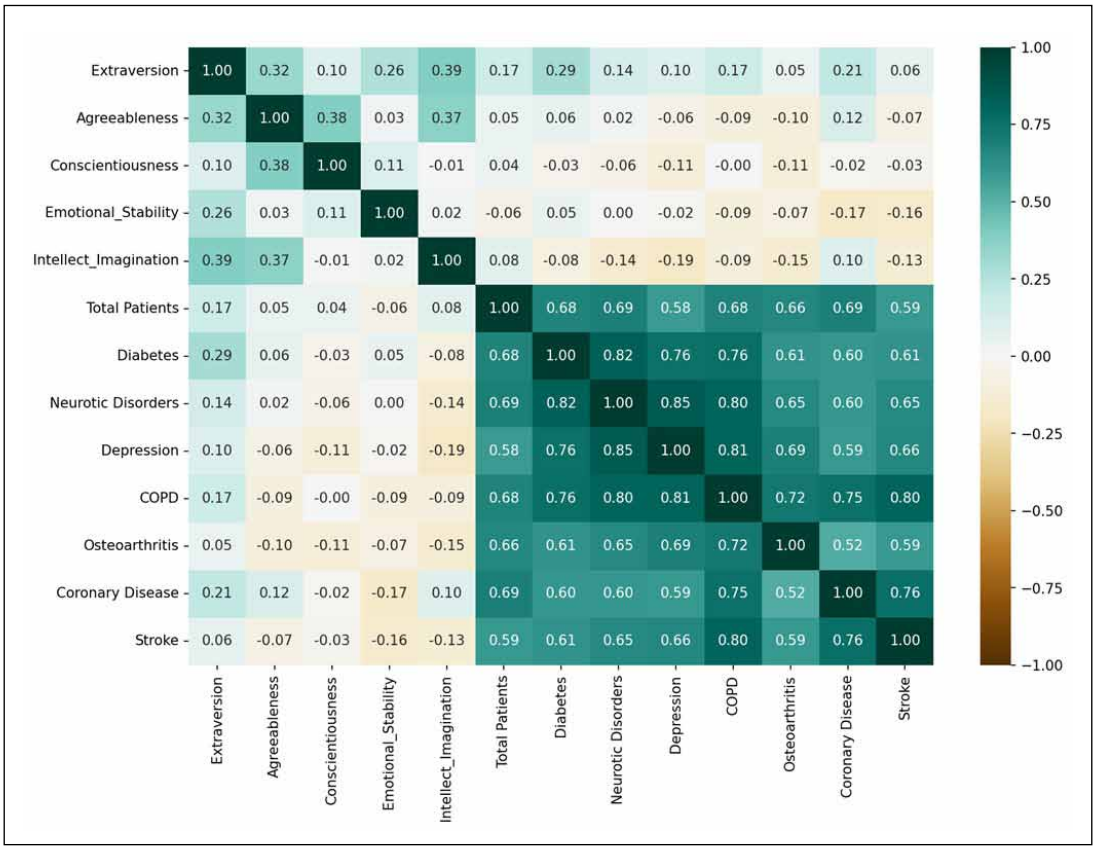

Figure 4: Correlations between Physicians' Personality Traits and Patient Groups.

Figure 4 presents a correlation heatmap illustrating the strength and direction of associations between physicians' personality traits (Extraversion, Agreeableness, Conscientiousness, Emotional Stability, and Intellect/Imagination) and the sizes of patient groups across different chronic disease categories, as well as total patient caseload. Correlation coefficients (Spearman's ρ) are displayed within each cell, with color intensity indicating the magnitude of the association. • The upper-left block of the matrix shows correlations among personality traits. These correlations are generally low to moderate, indicating that the Big Five dimensions are largely independent, consistent with personality theory. • The lower-right block displays correlations among patient groups. Here, correlations are consistently high and positive, reflecting the expected pattern that physicians with larger overall caseloads tend to manage higher numbers of patients across multiple chronic conditions. • The cross-block area—where personality traits intersect with patient groups—reveals mostly weak correlations, indicating limited direct association between physician personality and the size of disease-specific patient groups. • One notable exception is the positive correlation between Extraversion and diabetes (ρ ≈ 0.29), which is visibly stronger than other personality–disease pairings but still falls within the weak-to-moderate range. Overall, the heatmap visually reinforces the statistical conclusion that patient group sizes are strongly interrelated, while personality traits exhibit only modest and selective associations with patient profiles. ILLUSTRATIVE EXAMPLE: For example, the cell corresponding to Extraversion and diabetes shows a correlation coefficient of approximately ρ = 0.29, indicating that more extraverted physicians tend to report managing slightly higher numbers of patients with diabetes. However, this association is substantially weaker than the correlations observed between diabetes and other patient groups (e.g., diabetes and depression or COPD), which exceed ρ = 0.75. This contrast illustrates that disease co-occurrence and overall caseload size explain much more variance in patient numbers than physician personality traits, supporting the interpretation that personality functions as a contextual modifier rather than a primary determinant of patient distribution. Taken together, Figure 4 demonstrates that while physician personality traits may relate selectively to certain patient groups, the dominant structure of the data is driven by caseload size and disease clustering, rather than by individual psychological characteristics.

were observed between Conscientiousness, a trait commonly linked with structure, responsibility, and adherence to guidelines, and the number of patients with chronic conditions such as coronary heart disease. This finding may reflect the uniform application of clinical protocols across the PHC system, which likely minimizes the observable influence of individual personality variation in guideline-driven care. In this context, standardized treatment pathways may attenuate any potential effect of physician-level behavioral differences.

Similarly, Emotional Stability and Agreeableness did not correlate with higher numbers of patients present-

ing with psychosomatic conditions such as depression or anxiety-related disorders. Although previous studies have suggested that emotionally stable or empathetic physicians are more effective in managing patients with mental health needs [11], this was not supported by the present data. A possible explanation lies in the self-reported nature of patient estimation, the underdiagnosis of mental health conditions in primary care and the frequent involvement of specialist services, all of which may obscure subtle physician-related effects.

The higher Openness to Experience scores observed among male physicians may reflect generational or cultural factors rather than clinical preferences, although further qualitative research would be needed to explore these patterns in greater depth. The overall weak correlations shown in Figure 4 indicate that, while physician personality may exert a modest influence on patient composition, organizational characteristics of practices, population catchment profiles, referral mechanisms and health system design are likely to play more substantial roles [12].

The novelty of this study lies in its attempt to bridge two distinct domains, personality psychology and the epidemiology of care, within the real-world context of Greek primary health care. Although the results did not yield strong predictive models, they underscore the complex and multidimensional nature of physician–patient dynamics and highlight new avenues for interdisciplinary investigation. Importantly, the findings support a conceptualization of physician personality as a contextual modifier rather than a primary determinant of patient distribution in primary care.

Comparative Discussion with International Studies

The findings of the present Greek primary care study align with, but also meaningfully diverge from, prior international research examining the role of physician personality, interpersonal characteristics, and contextual factors in clinical practice. Overall, the comparison suggests that physician personality operates primarily as a contextual and relational modifier, rather than as a dominant determinant of patient composition or health outcomes.

McManus et al. (2004), in a large longitudinal cohort of UK physicians, demonstrated that personality traits, particularly Neuroticism and Extraversion, were strongly associated with stress, burnout and approaches to work, but not with objective measures of patient mix or disease epidemiology [13]. This is consistent with the present study, where Big Five traits showed minimal explanatory power for patient disease profiles ($R^2 = 0.196$ at best), reinforcing the idea that personality influences *how* physicians practice rather than *which* patients they treat.

In contrast, Hojat et al. (2011) reported a robust association between physicians' empathy and objective clinical outcomes among diabetic patients, including better HbA1c and LDL control [14]. While their study identified empathy as an independent predictor of outcomes, it is important to note a key methodological distinction: Hojat et al. relied on electronic health records and laboratory values, whereas the present study focused on self-reported patient composition and caseload distribution. Thus, the positive association observed in the Greek sample between Extraversion and diabetes caseload appears conceptually compatible with Hojat et al.'s findings, but reflects patient retention and relational continuity, rather than physiological disease control.

System-level explanations are strongly supported by Starfield et al. (2005), who demonstrated that population health outcomes are far more strongly shaped by primary care system characteristics, such as accessibility, continuity, and coordination, than by individual physician attributes [12]. The weak correlations observed in the present study directly reinforce Starfield's conclusion that structural determinants dominate over individual-level psychological factors in shaping epidemiological patterns in primary care.

Evidence from Wong et al. (2013) further supports this interpretation by showing that even temporary contextual disruptions, such as facemask use, can significantly reduce patients' perception of physician empathy and relational continuity [15]. This finding underscores that situational and organizational factors may outweigh stable personality traits in influencing patient–doctor relationships, a conclusion consistent with the limited predictive capacity of personality traits observed in the Greek data.

Finally, Barnsley et al. (1999) found that physician sex, specialty, and cohort were associated with communication style and empathic behaviors, but not with disease distribution or clinical caseload composition [16]. The present study similarly identified gender differences in Emotional Stability and Openness, without corresponding differences in patient disease profiles, reinforcing the conclusion that interpersonal style does not translate directly into epidemiological differentiation.

Taken together, these comparisons position the

present study firmly within the contemporary literature: physician personality matters, but primarily as a relational lens through which care is delivered, not as a driver of patient allocation or disease prevalence.

Future Research

Future research should build on the exploratory findings of the present study by adopting designs and data sources that allow stronger inference regarding the role of physician personality in primary care dynamics. A first and essential direction concerns the use of objective patient registry or electronic medical record (EMR) data, rather than physician self-estimates of caseload composition. Linking validated personality assessments of physicians with routinely collected administrative or clinical data would enable more precise measurement of patient volumes, diagnostic categories, follow-up frequency, and health outcomes, thereby reducing reporting bias and improving internal validity.

Second, longitudinal study designs are needed to examine whether physician personality traits predict patient-related processes over time. Such designs would allow researchers to move beyond cross-sectional associations and assess whether traits such as Extraversion or Emotional Stability are associated with patient retention, continuity of care, adherence to treatment, consultation frequency, or follow-up intensity across extended periods. Longitudinal data would also make it possible to explore potential bidirectional effects, whereby patient mix and workload may in turn influence physician behavior, well-being, or professional development.

Third, future work would benefit from mixed-method approaches that integrate quantitative analysis with qualitative inquiry. In-depth interviews or focus groups with physicians and patients could illuminate how personality traits interact with communication style, practice organization, team dynamics, and patient preferences in shaping care relationships. Such qualitative insights would help contextualize quantitative findings and clarify the mechanisms through which personality operates as a contextual modifier rather than a direct determinant of patient distribution.

Finally, expanding future studies to larger and more diverse samples, including different primary care systems and organizational models, would enhance generalizability and allow comparative analyses across health systems. Together, these directions would advance understanding of how physician personality interfaces with organizational and system-level factors, contributing to a more nuanced and evidence-based account of relational medicine in primary care.

Limitations

Several limitations should be considered when interpreting the findings of this study. First, the cross-sectional and exploratory design precludes causal inference. The observed associations between physician personality traits and patient caseload composition reflect contemporaneous patterns and cannot determine directionality or temporal dynamics. In addition, the relatively modest sample size, although adequate for exploratory analyses, limits statistical power and may have reduced the ability to detect small or condition-specific associations.

Second, the study relied on self-reported estimates of patient caseloads rather than objective clinical or administrative records. Although participating physicians are expected to have a reasonable overview of their regular patient populations, recall bias and estimation error cannot be excluded. This limitation is particularly relevant for conditions that may not be managed exclusively within primary care.

In this context, COPD warrants specific consideration. In Greece, as in many health systems, COPD diagnosis confirmation, staging, and long-term follow-up are frequently shared with or led by pulmonology specialists, especially for moderate to severe disease. As a result, COPD may be underrepresented in GP-reported caseloads, and the accuracy of self-reported COPD patient numbers at the primary care level may be reduced. Consequently, the absence of statistically significant associations between physician personality traits and COPD caseloads in the present study should not be interpreted as evidence of no relationship, but rather as a reflection of care pathway patterns and shared management arrangements that place part of COPD care outside routine GP caseload accounting.

Third, mental health conditions such as anxiety-related disorders and depression may also be underdiagnosed or variably coded in primary care, further attenuating detectable associations. Finally, unmeasured contextual factors, including practice organization, catchment population characteristics, referral norms, and regional service availability, may have influenced patient distribution independently of physician-level traits.

Taken together, these limitations reinforce the interpretation of physician personality as a contextual

modifier rather than a primary determinant of patient distribution and underscore the need for future studies using objective patient registries, longitudinal designs, and mixed-method approaches to more fully capture the complexity of primary care delivery.

CONCLUSIONS

This study examined the potential influence of physicians' personality traits on the composition of their patient populations in a primary care setting, with particular emphasis on chronic disease categories. The findings provide exploratory and preliminary evidence that Extraversion may be positively associated with the number of patients diagnosed with diabetes, suggesting that personality factors could modestly influence patient retention and communication dynamics in long-term care contexts.

However, the overall predictive power of personality traits was limited, and no consistent associations were observed for other conditions. These results suggest that organizational, health system–level, and population-related factors play a more influential role in shaping patient distributions within primary care.

From a clinical perspective, acknowledging physicians' interpersonal strengths and behavioral tendencies may facilitate more effective team allocation, medical training, and patient–doctor matching strategies, provided that such considerations are integrated alongside structural and organizational constraints of primary care delivery. From a research standpoint, future investigations using objective patient records, larger and more diverse physician samples, and longitudinal or mixed-method designs could further elucidate how personality influences care delivery and health outcomes.

In summary, while physician personality may not constitute a dominant determinant of clinical caseload, it remains a contextual modifier and an underappreciated dimension of professional identity, one that merits continued exploration within the framework of personalized and relational medicine.

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Applications of Digital PCR in Clinical Diagnostics and Therapeutic Monitoring

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Abstract

Digital polymerase chain reaction (dPCR) represents a transformative advancement in molecular diagnostics, offering enhanced sensitivity, specificity, and absolute quantification of nucleic acids. This narrative review explores the principles, advantages, and expanding clinical applications of dPCR, particularly in infectious disease diagnostics, oncology, and genetic screening. dPCR has demonstrated superior performance in pathogen detection, liquid biopsy for cancer prognosis, and prenatal genetic testing, surpassing conventional PCR techniques in precision and reproducibility. Furthermore, its resistance to inhibitors and multiplexing capabilities make it a valuable tool in clinical decision-making and personalized medicine. Despite its advantages, challenges such as cost, standardization, and clinical adoption remain barriers to widespread implementation. Continued technological advancements, including automation and high-throughput platforms, are expected to further integrate dPCR into routine clinical practice, ultimately improving patient outcomes.

Key words: *Digital PCR; molecular applications; clinical diagnostics.*

INTRODUCTION

The increasing complexity of modern healthcare challenges necessitates the development of innovative and robust molecular diagnostic techniques. Molecular analysis has become an indispensable tool in both preventive medicine and disease diagnosis, a fact that was particularly underscored by the COVID-19 pandemic. The need for highly sensitive and specific diagnostic methods has driven the continuous development of novel molecular techniques, as well as the refinement of existing technologies. Among these, polymerase chain reaction (PCR) stands out as the gold standard for pathogen detection due to its unparalleled accuracy in amplifying and identifying nucleic acids. PCR has played a pivotal role in the rapid detection of infectious agents such as SARS-CoV-2, enabling timely clinical decision-making and epidemiological surveillance. As molecular diagnostics continue to evolve, further advancements in PCR and related methodologies are expected to enhance diagnostic precision, efficiency, and accessibility, ultimately shaping the future of personalized and precision medicine.

Described by his inventor, Mullis, as the method that can detect "almost anything in anyone", it differs quite a bit from its original version with its evolutions taking up more and more space. Its most recent form, digital polymerase chain reaction (dPCR), had emerged as a useful methodology that is gaining more and more applications in prevention, diagnosis and treatment [1].

Basic Principles and Mechanisms

What is digital polymerase chain reaction and why is it considered special? It is a third-generation PCR reaction that enables absolute quantification of nucleic acids through the compartmentalization of the sample and the simultaneous execution of the same reaction in each individual compartment of the sample. Abol-

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ishing the semi-quantitative nature of simple PCR, it carries the possibility of direct monitoring of reactions with a time parameter, with greater accuracy overall and at individual stages of reactions, with immediate quantitative and qualitative recording even in complex samples, small quantities and rare genes [2]. Specifically, dPCR functions by dividing a sample into numerous micro-reactions, each containing zero, one, or a few target DNA or RNA molecules. The amplification of the target sequence occurs within these isolated partitions, followed by fluorescence-based detection of positive and negative partitions. The proportion of positive reactions is then used to determine the absolute nucleic acid concentration through Poisson statistical analysis [3]. This partitioning approach eliminates the need for standard curves, improving the accuracy and reproducibility of nucleic acid quantification compared to quantitative PCR (qPCR) [4].

dPCR provides several advantages over traditional PCR-based methods. One of its most significant benefits is absolute quantification, which does not require external reference standards, thereby reducing variability and improving consistency in results [5]. The high sensitivity and precision of dPCR make it particularly useful for detecting low-abundance targets, such as rare mutations in oncology and low viral loads in infectious disease diagnostics [6]. Additionally, dPCR exhibits robust resistance to inhibitors commonly found in biological samples, making it a superior choice for complex matrices such as blood, tissue, and environmental samples [7]. Furthermore, dPCR facilitates multiplexing, allowing the simultaneous detection of multiple genetic targets in a single reaction, which is particularly beneficial in clinical applications requiring comprehensive genetic profiling [8]. However, despite the automation it offers, user training is essential. The applications of this method are numerous and constantly increasing.

Applications in Microbiology

dPCR was extensively used during the COVID-19 pandemic and continues to be applied for detection of SARS-CoV-2, quantification of viral load, mutation detection, and monitoring of disease progression [9]. Besides COVID-19, assays have been used to quantify many viruses, including HIV DNA and HIV two-long terminal repeat (2-LTR) circles [10,11], CMV [12,13], hepatitis B virus [14], JC polyomavirus [15], human papillomavirus [16], HIV RNA [17- 19], human T-lymphotropic virus [17,18], human rhinoviruses [20], hepatitis C virus [19], hepatitis E virus [21], human parechovirus type 3 [22]. These assays have also been applied for the quantification of *Mycobacterium tuberculosis* [23], *Helicobacter pylori* [24] bacterial targets, and the malaria parasite [25]. The utility of dPCR is so substantial that you can use this technique not only for diagnosis, but also for the monitoring of these microbes in the community, by allowing the massive sample processing [26].

Applications in Oncology

Its application in liquid biopsy may represent the most promising clinical use of using dPCR for diagnosis and prognosis and this is evidenced by many different research efforts for a variety of malignancies. Research showed that levels of MACC1 and S100A4 gene derivatives were found to be elevated in ovarian cancer patients compared to healthy subjects (318 serum samples from 79 patients quantified by RT-qPCR and ddPCR) [27]. The increased levels of MACC1 and S100A4 were associated with an increased level of FIGO (advanced gynaecological cancer) and therefore the serological levels of these derivatives can be associated with early diagnosis, overall survival, but also evaluation of the effectiveness of CMT-type methods, surgical cytoreduction with quantitative measurement in serum of patients before and after the use of such methods [28].

Even in types of malignancy with great genetic heterogeneity, such as triple negative, or HER-2 NEG breast cancer, liquid biopsy with dPCR showed tremendous diagnostic benefit, as shown in a study by the Curie Institute of Dr. Carausu's team in patients with metastatic breast cancer of type HER-2 NEG that began a few years ago-2019. Specifically, in phase III, which includes 1000 patients from over 80 diagnostic centers with HER-2 negative metastatic breast cancer who have undergone endocrine therapy, mutations in genes associated with resistance to each treatment are detected using liquid biopsy and sample processing with dPCR [29]. A basic example is the detection with the help of dPCR real-time mutations in the ESR1 gene in thousands of ctDNA samples (circulating in the blood cancer DNA) before and after endocrine therapy or even after treatment change, an indicator that can be used as a prognostic or diagnostic biomarker [30].

Similar results have shown its use regarding the direct amount of EGFR variants from ctDNA in blood samples from non-small cell lung cancer in a plethora of studies, for example, Wang et al, in which dPCR was used for EGFR T790 gene detection. Clinically, it was shown that

T790M-positive patients have better clinical outcomes to EGFR-TKIs than T790M-negative patients, using it as a possible biomarker [31]. Even in cases where tumour cell purity and cellularity are significantly low, dPCR is sensitive enough to detect variants with low allele frequencies that are critical for determining malignancy (such as KRAS), identifying microRNAs (miRNAs), somatic variants, copy number variants, and methylation [32]. Renal cell carcinoma also falls into this category where Sequiera et al. managed to create a ddPCR-based panel to detect 4 circulating mi-RNAs (free RNAs with small amount nucleotides responsible for gene regulation and function). Renal carcinoma patients disclosed significantly higher circulating levels of hsa-miR-155-5p compared to healthy donors, whereas the opposite was observed for hsa-miR-21-5p levels. Furthermore, hsa-miR-21-5p and hsa-miR-155-5p panels detected RCC with high sensitivity (82.66%) and accuracy (71.89%). The hsa-miR-126-3p/hsa-miR-200b-3p panel identified the most common RCC subtype (clear cell, ccRCC) with 74.78% sensitivity [33].

Applications in Genetics and Prenatal Testing

This technique has already been used in prenatal testing as a non-invasive test for genetic diseases, utilizing cffDNA (cell-free fetal DNA), easily obtained from a maternal blood sample. Specific autosomal recessive diseases and predominant monogenic disorders in high-risk pregnancies, based on family history, parental carrier status, or fetal ultrasound findings can be diagnosed or monitored via dPCR, which can be used to detect abnormalities even when there is a small amount of DNA with low variation frequencies.

Firstly, fetal chromosomal aneuploidies can be detected with DPCR; Fan et al. estimated that the sensitivity of cdPCR is much higher than RT-PCR and fluorogenic quantitative PCR in the detection of fetuses with trisomy syndrome 21. In another study that looked at 283 clinical samples, non-invasive prenatal dPCR testing for trisomy 13, 18, and 21 in a single-tube assay showed 100% detection sensitivity and 95.12% specificity [34 - 36].

Second, in autosomal recessive disorders, dPCR has shown its strength early on since 2008, when dPCR was used to detect beta-thalassemia. Quantifying the mutated DNA of the mother and fetus could help diagnose pathogenic fetal genes [37,38]. Many years later, in 2016, Lee et al. detected both common and rare deletions in thalassemia using dPCR [39]. Even sickle cell disease (82% of male fetuses and 75% of female fetuses were diagnosed with SCD using DYS14, the specific marker of the Y chromosome marker) (HBB p.Glu6Val) [40] or spinal muscular atrophy (SMN1 and SMN2 with CVs of 1.7-3.7% and 2.1-2.7%, respectively) have been applied to prenatal screening using dPCR [41].

Comparative Performance of dPCR and Advanced Molecular Diagnostic Technologies

In the context of clinical diagnostics, dPCR has emerged as a valuable alternative and complement to traditional methods such as qPCR and next-generation sequencing (NGS). Compared to qPCR, dPCR offers superior sensitivity and precision, particularly in detecting low-abundance targets. This is critical in infectious disease diagnostics, where dPCR has demonstrated improved performance over qPCR in identifying low viral loads of pathogens such as SARS-CoV-2, often detecting cases missed by qPCR due to its lower limit of detection and greater tolerance to inhibitors [42, 43].

In oncology, dPCR outperforms qPCR in quantifying circulating tumor DNA (ctDNA) mutations with greater accuracy and reproducibility, making it especially suited for monitoring minimal residual disease and treatment response [44]. While NGS offers unparalleled breadth for mutation discovery and comprehensive profiling, dPCR excels in the targeted quantification of known variants. For instance, studies comparing ddPCR and NGS in detecting EGFR mutations in non-small cell lung cancer (NSCLC) report concordance rates above 90%, highlighting dPCR's utility as a reliable and cost-effective follow-up tool for high-throughput genomic analysis [45, 46]. Moreover, dPCR's faster turnaround time and simpler workflow compared to NGS make it an attractive choice for clinical settings requiring rapid, actionable results.

Emerging innovations are rapidly extending the clinical potential of dPCR. The advent of CRISPR-dPCR combines CRISPR-based sequence recognition with digital partitioning, enabling ultra-high specificity and sensitivity. For example, RADICA (Rapid DIgital Crispr Approach) has achieved absolute quantification of SARS-CoV-2 RNA in under an hour, four times faster than traditional dPCR, with equivalent accuracy, paving the way for rapid, precise viral diagnostics in clinical settings [47].

Parallel strides in point-of-care (POC) integration are transforming dPCR into portable, user-friendly formats. A smartphone-operated handheld dPCR device ("SPEED") demonstrates that thermal cycling, fluorescence detec-

tion, and data analysis can be miniaturized into a low-cost unit, with performance comparable to benchtop systems [48]. Such platforms are well-positioned for decentralized testing, a crucial requirement during infectious outbreaks or in resource-limited clinics.

In single-cell applications, microfluidic-based dPCR offers transformative insights into cellular heterogeneity. Reviews highlight its utility in quantifying gene expression and rare mutations from individual cells with high precision and throughput. In viral diagnostics, single-cell ddPCR has been used to identify HIV- or HBV-infected cells without DNA extraction, techniques that hold significant promise for early infection detection and therapy monitoring [49, 50].

These developments position dPCR as an adaptable technique that complements existing tools. CRISPR-dPCR excels in ultra-sensitive, rapid detection of known targets; POC systems bring this capability to the bedside or field; and single-cell dPCR addresses cellular-level diagnostics in oncology, immunology, and prenatal care. As these formats mature and accrue rigorous clinical validation, dPCR stands to play a pivotal role across precision medicine, infectious disease management, and point-of-care diagnostics.

Future Perspectives and Challenges

Despite its advantages, dPCR faces several challenges that hinder its widespread clinical adoption. One of the primary concerns is the high cost associated with dPCR instruments and reagents, which limits accessibility in resource-constrained settings. Additionally, there is a need for standardized protocols and regulatory guidelines to ensure consistency and reliability across different laboratories and clinical applications. The complexity of data analysis and interpretation also presents a barrier, necessitating the development of user-friendly software and bioinformatics tools to streamline workflows. Ongoing advancements in automation aim to address these limitations by enhancing the efficiency and scalability of dPCR platforms. The integration of microfluidics and droplet-based technologies has led to the development of high-throughput dPCR systems capable of processing large sample volumes with reduced reagent consumption. Furthermore, efforts to optimize assay designs and improve multiplexing capabilities are expected to expand the utility of dPCR in clinical diagnostics. The incorporation of dPCR into routine clinical practice also requires robust validation studies to demonstrate its clinical utility and cost-effectiveness compared to existing molecular techniques. As emerging research continues to refine dPCR methodologies, its potential to become a mainstream diagnostic tool will largely depend on collaborations between researchers, healthcare providers, and industry stakeholders to address these challenges and drive widespread implementation.

CONCLUSION

dPCR represents a transformative advancement in molecular diagnostics, offering exceptional precision, sensitivity, and the ability to provide absolute quantification of nucleic acids. Its proven utility in infectious disease diagnostics, oncology, and prenatal testing underscores its potential to reshape clinical decision-making. Compared to conventional PCR methods, dPCR demonstrates superior performance in detecting low-abundance targets, overcoming inhibitors, and enabling multiplex analysis in complex samples. However, despite its considerable promise, dPCR is not without limitations. High costs, limited scalability for high-throughput applications, and current constraints in multiplexing capacity pose significant barriers to widespread clinical adoption [51]. Moreover, the lack of standardized protocols and regulatory guidelines hinders integration into routine diagnostics and limits inter-laboratory comparability. Reducing operational costs and developing robust clinical validation studies will be essential for mainstream implementation. Interdisciplinary collaboration among clinicians, researchers, and regulatory bodies is also critical to establish evidence-based guidelines and ensure that dPCR transitions effectively from a specialized research tool into a routine component of precision medicine. With continued innovation and systemic support, dPCR holds strong potential to become a cornerstone in next-generation diagnostics, ultimately improving patient care and clinical outcomes.

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Paraneoplastic Syndromes Across Organ Systems: A Literature-Based Diagnostic Guide

Dimitra Taprantzi

Abstract

Paraneoplastic syndromes (PSs) are rare and often under-recognized cancer-related conditions resulting in tissue or organ disorders distant from the primary tumor and its metastases. These syndromes reflect systemic effects of malignancies that are not attributable to direct tumor invasion, compression, or metastasis. Recent medical data have improved our understanding of these syndromes, but the majority of them are still difficult to diagnose due to their protean manifestations and overlapping features with other diseases. They are a diverse group of clinical symptoms that can affect the neurological, endocrine, dermatological, gastrointestinal, and hematologic systems, and therefore our knowledge of these syndromes is helpful in the diagnosis and treatment of the related tumor. In many cases PS occur concurrently with the diagnosis of the underlying malignancy but in others, they can be a harbinger of a growing undiagnosed neoplasm and thus the skills of a medical doctor are challenged. Timely recognition of PS not only facilitates early diagnosis of potentially curable malignancies but also helps to avoid mismanagement of symptoms. This review focuses on the diagnosis and potential mechanisms of the most known paraneoplastic syndromes, highlighting the importance of interdisciplinary evaluation and immunological testing.

Key words: *Paraneoplastic syndrome; symptoms; diagnosis; endocrine; neurologic; hematologic; dermatologic; malignancies*

INTRODUCTION

Paraneoplastic syndromes (PS) are a diverse group of symptoms that arise as a result of a neoplasm, but which cannot be directly assigned to the primary malignancy and its metastases. Although PS are well known, establishing a diagnosis of the PS itself and the underlying malignancy is challenging. Their clinical presentation often mimics primary autoimmune, infectious, or degenerative conditions, which may result in delayed or missed diagnosis. In some instances, PS can precede the development of a tumor up to five years, potentially enabling the early diagnosis of a curable malignancy [1]. According to our current knowledge, some of the known PS arise by different mechanisms, such as secretion of antibodies and cross-reaction between normal host cells and tumor cells, secretion of peptides and hormones of the tumor but in the majority of them, there are limited data to explain their pathophysiology. In particular, immunological dysregulation involving both humoral and cellular immune responses appears to play a pivotal role in the development of these syndromes. PSs may affect diverse organ systems such as neurological, endocrine, dermatologic and hematologic system [2].

A literature review shows that PSs occur in up to 8% of patients with a malignancy [3]. This figure may be underestimated due to the complexity and variability

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of clinical manifestations, as well as underreporting in clinical practice. In view of the above, the purpose of this review is a practical approach of the diagnosis of the most known paraneoplastic syndromes. By categorizing them according to the organ systems involved and exploring their immunopathogenic basis, this review aims to enhance clinicians' ability to recognize, investigate, and manage these rare but clinically significant conditions.

METHODOLOGY

This review is based on data extracted from peer-reviewed publications indexed in PubMed. Emphasis was placed on selecting literature published within the past 15-20 years to ensure the inclusion of the most current and clinically relevant information. The analysis focused on paraneoplastic syndromes that are well-established and commonly encountered in clinical practice.

Neurological Paraneoplastic syndromes

The pathophysiology of the paraneoplastic neurological syndromes (PNS) is not totally understood, but immunological mechanisms are most possibly involved. There is strong evidence that antibodies and T-cells fight against antigens expressed on the malignancy, but some of these antigens also reside in cells of the nervous system [4]. This immunological cross-reactivity leads to an autoimmune attack against components of the central and peripheral nervous systems, resulting in various neurological deficits.

Antibodies related to PNS may be found either in plasma or cerebrospinal fluid and are categorized in two groups: antibodies against intracellular neuronal antigen (previously known as onconeuronal antibodies) and antibodies against cell surface or against synaptic proteins. Onconeuronal antibodies are divided in well-characterized and partially characterized. Well-characterized antibodies are those that are strongly associated with a tumor, and the most known are anti-Hu, Yo, CV2, Ri, Ma_2a, and anti- amphiphysin. Partially characterized antibodies are those that are not specifically correlated with a special type of tumor and these are anti-Tr, ANNA3, PCA2, Zic4, and mGluR1. These antibodies can guide diagnosis and may serve as biomarkers to identify occult malignancies, particularly when clinical presentation is atypical.

PNSs can affect the central nervous system, peripheral nervous system and neuromuscular junction and muscle. The most usual PNSs are Lambert-Eaton myasthenic syndrome and Guillain-Barré syndrome [5]. Other common manifestations include subacute cerebellar degeneration, limbic encephalitis, and encephalomyelitis, which may present with cognitive changes, psychiatric symptoms, or seizures.

In 2004, a panel of experts recommended diagnostic criteria for PNSs and a few years later the diagnostic criteria were updated by the PNS-care panel of experts [6]. According to 2004 criteria, the PNSs are divided into classical and non-classical syndromes. Neurologic diseases that have been found to be strongly correlated with malignancies are included in Classical PNSs. Classical PNS of central nervous system include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration and opsoclonus-myoclonus, classical PNS of peripheral nervous system are subacute sensory neuropathy and chronic gastrointestinal pseudo obstruction and classical PNS of neuromuscular junction and muscle include Lambert-Eaton myasthenic syndrome and dermatomyositis.

According to the panel, there are three aspects of evidence required to characterize a PNS as definite or possible: the presence of a classical neurological syndrome, a confirmed tumor diagnosis and the detection of well-characterized onconeural antibodies [6]. Specifically, in order to characterise a syndrome as definite, it should satisfy one of the following criteria: a) by the time of making diagnosis of a classical PNS, cancer should appear within the following five years, b) neurological disease that it is not included in the list of classical PNS which does not resolve spontaneously but it resolves with malignancy treatment, c) non-classical PNS with positive onconeuronal antibodies and appearance of the malignancy within the following five years and d) neurological disease with positive well-characterized onconeural antibodies and no evidence of cancer's existence.

Possible PNSs could be a) classical PNS with negative antibodies, b) neurological syndrome with positive partially characterized antibodies and no proof of malignancy, and c) non – classical neurological disease with negative antibodies and appearance of a tumor within the following two years.

In 2021, the panel changed the definition of classical and non-classical syndromes and introduced a more refined stratification system. They divided PNS into three categories (definite, probable and possible) using the PNS-care score, which combines the clinical symptoms with the presence of certain antibodies and

the presence of malignancy in imaging testing as shown in Table 1 [7]. According to the PNS scoring system PNS is definite when the score is above 8, probable when the score is between 6 and 8, possible when it is 4 or 5, and there is no possibility of the clinical symptom being a PNS when the score is lower than 4. This structured approach improves diagnostic accuracy, minimizes overdiagnosis, and supports clinical decision-making.

The use of the PNS scoring system requires appropriate categorisation of antibodies and clinical symptoms. The antibodies are divided into three categories according to their frequency of cancer involved as shown in Table 2 [8]. Some neurological clinical presentations have been categorised into high-risk, intermediate risk and low risk phenotypes. High risk phenotypes are known also as classical PNS (according to 2004 guidelines) and they are strongly connected to malignancy presence. These are encephalomyelitis, limbic encephalitis, rapidly progressive cerebellar syndrome, opsoclonus-myoclonus, sensory neuronopathy, gastrointestinal pseudo-obstruction (enteric neuropathy) and Lambert-Eaton myasthenic syndrome. Intermediate-risk phenotypes are conditions associated with the presence of a tumor and warrant investigation when no other cause is found. These are encephalitis, Morvan syndrome, myelopathy, Stiff-person syndrome and polyradiculoneuropathies [7]. A combination of clinical judgment and the scoring system plays a vital role in uncovering hidden malignancies. Recognition of these risk phenotypes is crucial in the early detection of hidden cancers, particularly in neurologically unexplained or refractory syndromes.

A combination of thorough clinical judgment, immunologic testing, imaging studies, and the PNS scoring system plays a vital role in uncovering underlying malignancies and directing timely therapeutic interventions. Multidisciplinary collaboration between neurologists, oncologists, and immunologists is essential for optimal patient outcomes.

Paraneoplastic Endocrine Syndromes

The majority of endocrine PSs are a result of secretion of bioactive substances from malignant cells. The tumor can be of endocrine or non-endocrine origin. Lung, colon, skin and breast cancer are the most common cancers connected to endocrine PSs. These syndromes are often the result of ectopic hormone production, in which tumor cells acquire the ability to synthesize and secrete peptide hormones or hormone-like substances that mimic physiological processes, leading to distinct clinical presentations.

The most common PSs in this category are syndrome of inappropriate anti-diuretic hormone secretion (SIADH), Cushing's syndrome, hypoglycaemia, and hypercalcemia. The severity of clinical symptoms is not correlated with the malignancy's stage.

SIADH is a result of hypersecretion of inappropriate anti-diuretic hormone ADH and it usually appears with euvolemic hyponatremia, small cell lung cancer is one of the most common malignancies causing SIADH. ADH activates ADH receptor 2 (V2) located on the basolateral membrane of renal collecting duct cells to enhance the water permeability of the apical membrane and thus water reabsorption [9]. In normal circumstances the hypersecretion of ADH is controlled by osmoreceptors that try to maintain plasma osmolality within normal limits. In cancer patients, ADH secretion is not fully suppressed and ectopic production of ADH may

Table 1. *PNS-scoring system.*

Clinical level	High-risk phenotype	3	**Diagnosis**
	Intermediate risk phenotype	2	
	Phenotype not included in high risk or intermediate risk	0	
Antibodies	High-risk	3	**Definite:>/8** **Probable:6-7** **Possible:4-5** **NonPNS: /<4**
	Intermediate-risk	2	
	Low-risk	0	
Cancer	Found	4	
	Not found but follow up is no more than 2 years	1	
	Not found and follow up is more than 2 years	0	

Table 2. *Classification of antibodies associated with paraneoplastic neurologic syndromes.*

High risk (>70% associated with cancer)	Intermediate risk (30%-70% associated with cancer)	Low risk (<30%associated with cancer)
anti-Yo	anti-GABAβR	anti-LGI1
anti-Hu	anti-AMBAR	anti-DPPX
anti-Ri	anti-NMDAR	anti-GlyR
anti-Tr	anti -CASPR2	anti-mGluR1
anti-PCA	anti-mGluR5	anti-GABAAR
anti-CV2	anti-P/Q VGCC	anti-CASPR2
anti-KLHL		anti-GlyR
anti-Tr		anti-MOG
anti-SOX1		
anti-amphiphysin		

also occur [10], leading to euvolemic hyponatremia. If left untreated, this condition can result in neurological symptoms, including seizures and altered mental status.

Another very common endocrine PS is hypercalcemia. Hypercalcemia of paraneoplastic origin is neither a result of bone metastases nor a result of direct dysfunction of the parathyroid gland [11]. It occurs because of the secretion of PTH-related protein, which binds to the PTH receptor, and it is most commonly connected to squamous cell tumors and small cell lung cancer (SCLC) and more rarely in GI-NETs, phaeochromocytomas and carcinoid tumors. Additionally paraneoplastic hypercalcemia can be a result of ectopic production of 1,25-dihydroxy (OH)2 vitamin D and it is usually associated with hematologic malignancies [12]. This form of hypercalcemia may be severe and refractory to standard treatments, necessitating aggressive interventions.

Cushing's syndrome is also a common endocrine PS. A total of 10% of people with Cushing syndrome are considered to have a malignancy. It is caused by abnormal tumor production of adrenocorticotropic hormone (ACTH) or more rarely of corticotrophin-releasing hormone (CRH). Different types of lung malignancies are the most common tumors being associated with Cushing's syndrome (bronchial carcinoids, SCLC] [13]. Tumors with neuroendocrine cells of the thymus or pancreas are also connected to PS Cushing's syndrome [14]. The resultant hypercortisolism leads to classical signs such as central obesity, hypertension, glucose intolerance, and muscle weakness, which can significantly impair patient quality of life.

Another rare clinical endocrine PS is hypoglycaemia. The most common mechanism is ectopic production of insulin by islet (e.g. insulinoma) and non-islet tumors (e.g., gastrointestinal stromal tumors) [15]. Another possible mechanism is the secretion of peptides like insulin-growth factor 1 and 2 (IGF-1 and IGF-2, respectively), which bind to insulin receptors [16]. Additionally, in some cases, hypoglycaemia is a result of autoimmune mechanisms, involving the production of autoantibodies that stimulate insulin receptors [17]. Hypoglycaemia can be life-threatening if not promptly identified and treated.

In all cases, the endocrine manifestations of PS can obscure the underlying malignancy and may lead to delays in cancer diagnosis. Therefore, awareness of these paraneoplastic phenomena and their biochemical profiles is critical for early recognition and comprehensive management.

Paraneoplastic dermatologic syndromes

Dermatologic manifestations are a significant component of PS. These cutaneous signs may precede, coincide with, or follow the diagnosis of cancer, and they often provide valuable diagnostic clues. Necrolytic migratory erythema (NME), also called glucagonoma syndrome because its appearance is connected to this tumor, is a skin rash consisting of erythematous plaques in the perineum, upper and lower extremities and face. In due course the lesions increase in size and their borders become crusting. NME and hair loss are common symptoms presenting simultaneously in glucagonoma [18]. This syndrome is frequently accompanied by other systemic symptoms such as weight loss, glucose intolerance, and anemia, and its presence should prompt evaluation for pancreatic neuroendocrine tumors.

Acanthosis nigricans maligna is another dermatosis connected with malignancies. Dark symmetrical hyperpigmented skin areas of sudden onset usually appear in the axilla, groin, and cervical regions. A small percentage of patients have hyperpigmentation of the palms, and this condition is called tripe palms. This type of dermatoses relates to breast, liver, pancreas, gastric and ovarian cancer. Its appearance is associated with poor prognosis. Histologically, these lesions are characterized by papillomatosis, hyperkeratosis, and basal layer hyperpigmentation. Cytokines produced by the malignancy seem to have a pivotal role in fibroblast and keratinocyte stimulation [19].

Another form of acanthosis nigricans is the Leser -Trelat sign [20], which is the abrupt appearance of multiple seborrheic keratoses usually appearing in the upper part of the body. It is connected with gastric and colorectal carcinoma, other abdominal malignancies and less often with lymphomas [21, 22]. This phenomenon is believed to be mediated by epidermal growth factors released by the tumor, and recognition of this sign should prompt a thorough search for underlying malignancy.

Paraneoplastic pemphigus is a usual malignant dermatosis connected to haematological diseases such as non-Hodgkin lymphoma, chronic lymphocytic leukaemia and thymoma. Painful erosive areas and ulcers appear throughout the body as a result of IgG-mediated mechanism. More specifically autoantibodies bind to desmosomes and disrupt the connection between keratinocytes [23]. It has a poor prognosis, and the mortality rate reaches 90%.

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by painful plaques accompanied by fever, arthralgias and increased inflammatory markers. There are diagnostic criteria. To establish a diagnosis of Sweet, two major and at least two minor criteria are typically required. Major criteria are abrupt onset of painful nodules and characteristic neutrophil infiltration without vasculitis on biopsy. Minor criteria are temperature above 38, association with an underlying malignancy or an inflammatory response, elevated inflammatory markers (leukocyte count above 10.000, ESR above 20, increased CRP), and a great response to glucocorticoids [24]. Sweet syndrome may be associated with haematologic malignancies such as acute myeloid leukaemia, or with solid tumors such as breast or gastrointestinal cancer.

Dermatomyositis (DM) patients present with a variety of skin manifestations. They exhibit flat papules on extensor surfaces (elbows and hand joints) called Gottron papules accompanied by proximal muscle weakness (50% of the patients). A heliotropic eruption of the periorbital area is another pathognomonic feature of DM. It appears as an erythematous rash affecting the upper eyelids with or without periorbital oedema. In 1975, the Bohan and Peter criteria were established to facilitate the diagnosis of dermatomyositis as shown in Table 3 [25]. The association of DM with malignancies such as ovarian, pancreatic, and gastric carcinomas, as well as non-Hodgkin lymphomas, makes malignancy screening a vital component of DM workup [26, 27].

Paraneoplastic hematologic syndromes

Paraneoplastic eosinophilia, granulocytosis and thrombocytosis are common hematologic disorders in malignancies. The above are the result of the production of cytokines and other substances such as interleukin-5 (IL-5), Granulocyte colony-stimulating factor (G-CSF) and interleukin-6 (IL-6) respectively [28]. These hematologic abnormalities may serve as indirect indicators of tumor activity and can sometimes resolve with successful treatment of the underlying malignancy.

Pure red cell aplasia is also a common paraneoplastic manifestation in various malignancies. It is characterized by a marked reduction or absence of erythroid precursors in the bone marrow, leading to normocytic normochromic anaemia. This condition has been observed particularly in association with thymoma, and in some lymphoproliferative disorders [29].

Migratory thrombophlebitis, also known as Trousseau's syndrome because it was first described by the French internist Armand Trousseau, is characterized by thrombosis in unusual sites and is connected to the hypercoagulable state of malignancies [2]. Trousseau's syndrome frequently affects deep veins of the limbs, but also involves visceral and cerebral vessels, and is most commonly associated with pancreatic, lung, and gastric adenocarcinomas. Its pathogenesis is attributed to tumor-related production of procoagulant factors, mucins, and cytokines, leading to platelet activation and fibrin deposition [2]. Early identification of such abnormalities may guide physicians to investigate for occult malignancies, particularly when standard risk factors for thrombosis or cytopenia are absent.

Table 3. *Bohan and Peter classification criteria for dermatomyositis.*

CRITERIA	DIAGNOSIS
1. Proximal muscle weakness	DEFINITE: 5TH + 3 OF 1-4
2. Muscle biopsy showing myositis	PROBABLE: 5TH + 2 OF 1-4
3. Increased muscle enzymes	POSSIBLE: 5TH + 1 OF 1-4
4. EMG (electromyography) characteristic for myositis	
5. Typical rash (heliotrope rash, Gottron's sign)	

Disseminated intravascular coagulation (DIC) is a rare paraneoplastic syndrome characterized by the triad of prolongation of coagulation times, thrombocytopenia and hypofibrinogenemia [30]. It results from widespread activation of the coagulation cascade, leading to both thrombotic and bleeding complications. DIC is most commonly associated with haematological and non-haematological malignancies, especially mucin-secreting adenocarcinomas. The presence of DIC in a cancer patient is associated with poor prognosis and requires urgent management.

Autoimmune hemolytic anemia (AIHA) is another paraneoplastic phenomenon usually found in hematologic malignancies such as lymphomas but there have also been incidents of AIHA in patients with solid tumors. The majority of AIHA is caused by warm antibodies (IgG-mediated) and less often provoked by cold antibodies (C3-mediated) [31]. AIHA may present with pallor, jaundice, fatigue, and splenomegaly, and requires both immunosuppressive and tumor-directed therapies.

In addition, cancer-associated microangiopathic hemolytic anemia (CA-MAHA) is another PS in which peripheral blood smear shows red cell schistocytes with negative direct and indirect Coombs tests. It leads to obstruction in small vessels and platelet consumption [32]. This life-threatening condition is characterized by haemolysis, thrombocytopenia, and end-organ damage, mimicking thrombotic thrombocytopenic purpura (TTP). It is most often associated with disseminated gastric, breast, or lung carcinoma and usually carries a dismal prognosis.

Overall, hematologic paraneoplastic syndromes may be the initial or sole manifestation of malignancy. They often require prompt recognition and interdisciplinary coordination between haematologists and oncologists to manage both the syndrome and the underlying tumor. Continued vigilance and comprehensive laboratory evaluation are critical when confronted with unexplained hematologic abnormalities.

CONCLUSION

From all the above, it is obvious that PSs cover a great range of clinical and laboratory findings. The manifestation of characteristic clinical symptoms in certain paraneoplastic syndromes should prompt clinicians to consider an underlying malignancy, thereby facilitating earlier diagnosis, timely intervention, and improved patient prognosis. These syndromes often act as a biological "early warning system," particularly in the absence of obvious tumor-related signs. Their identification can significantly alter the clinical trajectory and improve patient outcomes.

Paraneoplastic antibodies hold significant potential as biomarkers for the early detection of underlying malignancies. Their presence may serve as a crucial diagnostic clue, prompting clinicians to initiate timely investigations for occult cancers. By incorporating antibody screening into the diagnostic workup of patients with unexplained neurological or systemic symptoms, healthcare providers may improve early cancer identification, enabling earlier intervention and potentially enhancing patient outcomes. Moreover, advances in serologic profiling and imaging have led to the development of scoring systems, such as the updated PNS criteria, that offer structured, evidence-based approaches to diagnosis.

The optimal approach to treating PSs involves not only addressing the associated symptoms but also eradicating the underlying malignancy. In oncology, new treatments are continuously emerging, offering hope that malignancies, and the paraneoplastic syndromes associated with them, particularly those with poor prognoses, may become more effectively treatable. Immunotherapies and molecularly targeted agents have already shown success in altering tumor behaviour and may indirectly lead to the resolution of paraneoplastic manifestations.

Further research is imperative to unravel the complex immunological and molecular mechanisms underlying these syndromes. Potential areas of study include the discovery of novel antibodies, the refinement of predictive scoring tools, and the development of immunomodulatory therapies specifically tailored for PS. A multidisciplinary approach that bridges oncology, immunology, neurology, and dermatology is essential for future progress.

In conclusion, heightened clinical suspicion, a systematic diagnostic framework, and ongoing research collaboration are the cornerstones of improving outcomes for patients with paraneoplastic syndromes.

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The Role of Revascularization in the Management of Patients with Chronic Coronary Syndrome: Focus on Percutaneous Coronary Intervention

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Abstract

Coronary artery disease (CAD) remains a global health burden and presents in the form of acute and chronic coronary syndromes. The management of chronic coronary syndromes (CCS) aims to relieve symptoms, improve quality of life and reduce the occurrence of major adverse cardiac events including death, myocardial infarction and cardiac-related hospitalizations. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are the key revascularization strategies. Current European and American guidelines suggest revascularization in high-risk patients such as those with uncontrolled symptoms, multivessel disease, left main disease or reduced left ventricular function. PCI is favored in patients with high surgical risk while CABG is favored in complex cases. Several landmark trials have assessed the role of PCI in CCS during the last decades. While PCI improves angina symptoms and quality of life, its impact on event-free survival remains unclear. Recently, subgroup analyses and meta-analytic data suggest that PCI may reduce spontaneous myocardial infarction and cardiac mortality especially in high-risk patients. In contrast, CABG in complex coronary artery disease and left ventricular dysfunction, has been proven to confer long-term survival benefits. This review provides a concise summary of current evidence regarding the additive value of revascularization, in particular PCI, on top of optimal medical therapy.

Key words: *Coronary artery disease; percutaneous coronary intervention; coronary artery bypass grafting; medical therapy; angina*

INTRODUCTION

Chronic coronary syndrome (CCS), formerly known as stable coronary artery disease (CAD), is one of the principal manifestations of cardiovascular disease, and thus, a major health burden worldwide [1]. The term CCS was introduced by the European Society of Cardiology (ESC) in the 2019 guidelines for stable CAD to better describe the clinical demonstration of CAD symptoms in periods where the patient is stable or after an acute coronary manifestation syndrome [2]; the American College of Cardiology (ACC) and the American Heart Association (AHA) used the respective term chronic coronary disease (CCD). Although patients classified with CCS may include different categories and presentations, the main category includes patients with angina or

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dyspnea, which may also be accompanied by reduced left ventricular ejection fraction (LVEF).

Treatment of CCS (medical therapy and coronary/myocardial revascularization) focuses on alleviating symptoms, improving quality of life and reducing the possibility of future major adverse cardiac events such as cardiac death and myocardial infarction [3]. Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) constitute the two modalities of myocardial revascularization in specific populations. Landmark studies such as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) [4], and recently, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) [5], have provided insights into the incremental value of myocardial revascularization in the clinical setting. However, it is not clear whether revascularization, in particular PCI, on top of medical therapy is associated with clinical benefit compared to optimal medical therapy alone. Several factors may influence the decision to proceed with revascularization, including the severity of ischemia, the complexity of coronary anatomy and the presence of comorbidities.

This review aims to present concise data regarding the value of coronary revascularization, in particular PCI, over medical therapy in patients with CCS, taking into account the current guidelines and recommendations, and exploring the potential benefit in specific patient populations according to available clinical data.

European and American Guidelines for Revascularization in CCS

According to the latest 2024 ESC guidelines for the management of patients with CCS, revascularization with either PCI or CABG is recommended for angina-related symptoms that are resistant to medical therapy (Class I Level A) [6-8]. In patient groups with left main disease or three-vessel disease, especially those with left ventricular dysfunction (EF ≤35%), randomized clinical trials (RCTs) and meta-analyses have shown superior outcomes for CABG compared with medical therapy alone (Class I Level B) [9-14]. In patients with high surgical risk, PCI may be considered as an alternative to CABG (Class IIb Level B), offering primarily symptom relief [15]. In patients with normal LV function, who have functionally significant left main stenosis (Class I Level A) [16,17], three-vessel disease (Class I Level A) or single-/two-vessel disease involving proximal LAD (Class I Level B) [18-23], revascularization has incremental value over medical therapy. CABG is considered to be superior to PCI in patients with multivessel disease, diabetes or higher complexity of CAD (Class I Level A) [24,25].

The AHA/ACC Joint Committee uses the term CCD instead of CCS as mentioned above. The AHA/ACC 2023 guidelines also emphasize the importance of revascularization in patients with symptomatic CCD who do not respond to guideline-directed medical therapy (Class 1 Level A) [8,26-28]. In those with CCD and LV dysfunction, who have left main disease or multivessel disease, CABG is better than medical therapy alone (Class 1 Level B-R) [10,14,29]. To reduce the possibility of major cardiovascular events, revascularization should be considered in patients with CCD and multivessel disease (Class 2a Level B-R) [18,19,23,30-32]. In patient groups with diabetes [33] or more complex coronary anatomy, CABG generally offers better outcomes compared to PCI (Class 1 Level A) [34], but PCI should be considered in those with high surgical risk (Class 2a Level B-NR).

According to the ESC (2024) and AHA/ACC (2023) guidelines, the use of revascularization is strongly supported in high-risk populations such as those with left main disease**,** multivessel disease, and left ventricular dysfunction, with a clear preference for CABG in more complex cases and PCI as a viable alternative in high-risk surgical candidates. Table 1 provides a comparative summary of the main recommendations in these guidelines regarding the role of revascularization in improving survival/prognosis.

Angina and Quality of Life

Angina, one of the most common symptoms in patients with CCS, elicits a significant impact on quality of life (QoL). Extensive studies and systematic analyses have demonstrated the pivotal role of revascularization in alleviating these symptoms and enhancing patient outcomes.

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial evaluated 5,179 participants with chronic CAD and moderate or severe ischemia, comparing an initial invasive treatment strategy (catheterization ± revascularization) to an initial conservative strategy [5]. The ISCHEMIA research program included a 3-, 12-, 24- and 36-month follow-up QoL substudy which concluded that patients experiencing more frequent episodes of angina derived significant benefits from an

Table 1. *Comparative summary of recommendations in the ESC and ACA/AHA/SCAI guidelines for revascularization in order to improve survival/prognosis.*

ESC Guidelines 2024		
	CABG	PCI
LVEF>35%		
Left Main disease	I	I
Multivessel disease	I	I
1-2VD with proximal LAD	I	I
LVEF≤35%	I	IIb
ACC/AHA/SCAI Guidelines 2023		
	CABG	PCI
Left Main disease	I	I / IIa*
Multivessel CAD		
LVEF<35%	I	I
LVEF 35-50%	IIa	I
LVEF>50%	IIb	IIb
Proximal LAD	IIb	IIb

*If high anatomic complexity and patient not suitable for CABG, then Heart Team discussion has a class I recommendation to decide medical therapy +/-PCI. If there is not high anatomic complexity, then PCI has a class IIa recommendation.

Abbreviations: ACC/AHA/SCAI; American College of Cardiology/ American Heart Association/ Society of Cardiovascular Angiography and Intervention, ESC: European Society of Cardiology, CAD: Coronary Artery Disease, LAD: left anterior descending artery, CABG: coronary artery bypass grafting, PCI: Percutaneous Coronary Intervention, LVEF: Left Ventricular Ejection Fraction, VD: vessel disease.

invasive strategy. The average difference in the 19-item Seattle Angina Questionnaire (SAQ) summary score (an angina frequency score that measures health status related to CAD; scores range from 0 to 100 with higher scores indicating fewer symptoms and better health status) showed benefit in the invasive arm, with a mean increase of 1.4 points (95% CI: 0.2-2.5) across all follow-up periods. Among the 744 patients with more frequent angina at baseline (SAQ Angina Frequency score <80), those assigned to the invasive strategy achieved a mean 3.7-point higher score on the 19-item SAQ Summary compared to the conservative strategy group (95% CI: 1.6-5.8). Physical limitations (based on the Duke Activity Status Index score) increased by 3.2 points (95% CI: 0.2–6.1), angina frequency improved by 3.2 points (95% CI: 1.2-5.1), and QoL/Health Perceptions showed a gain of 5.3 points (95% CI: 2.8-7.8) in the invasive group compared to the conservative group. The invasive strategy was associated with marked improvements not only in angina-related symptoms but also in overall quality of life, encompassing enhanced physical functioning and psychological well-being [35].

The value of percutaneous revascularization in improving symptoms was further highlighted in the Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA-2) trial [7]. In this trial, 301 patients with stable angina receiving minimal or no pharmacological therapy underwent revascularization treatment compared to another group that underwent a placebo intervention (i.e., no revascularization). At the 12-week follow-up, the PCI group had a mean angina symptom score of 2.9 compared to 5.6 in the placebo group, with an odds ratio of 2.21 (95% CI: 1.41-3.47, p<0.001). The outcomes of this trial demonstrated substantial benefits in terms of angina relief and quality of life improvement in these patients.

Beyond "stent-assisted angioplasty", CABG also plays a crucial role in angina relief. It has been demonstrated that the relief of anginal symptoms and improvement in quality of life become evident early and remain significant over a four-year follow-up period. Zhang et al. assessed cardiac-specific health status using the SAQ at baseline and at 6- and 12-months post-revascularization in patients randomized to either stent-assisted PCI with 488 patients or CABG with 500 patients as part of the 'Stent or Surgery' trial [36]. Significant improvements in physical limitation, angina frequency, and quality of life scores were observed in both the PCI and CABG treatment groups. At 6 months, scores improved within a range of 13.6 to 34.7 points, and at 12 months, the range was 14.3 to 38.2 points, with all changes being statistically significant (p<0.001). Brorsson et al. conducted a prospective survey and reviewed medical records of 601 Swedish patients with stable angina and one- or two-vessel disease [37]. The cohort included 252 patients who underwent CABG and 349 who underwent PCI. At 6 months, patients who underwent bypass surgery showed greater improvements compared to those who had angioplasty in physical functioning (15.3 vs 10.5, p<0.05) and general health perception (16.5 vs 10.2, P<0.05). Additionally, at 21 months, patients in the CABG group experienced better pain relief (19.4 vs 14.6, p<0.05), improved quality of sleep (17.6 vs. 4.6, p<0.05), and enhanced general health perception (17.3

vs. 12.1, p<0.05). However, by the 48-month follow-up, these differences were no longer observed between the two groups.

Bangalore et al. conducted a systematic review and meta-analysis examining routine revascularization in patients with stable ischemic heart disease [8]. They concluded that the invasive strategy not only alleviates anginal symptoms (relative risk [RR]: 1.10, 95% CI: 1.05-1.15) but is also associated with a reduced risk of future episodes of unstable angina (RR 0.64, 95% CI: 0.45-0.92).

The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation-2 (FAME 2) trial compared PCI guided by fractional flow reserve (FFR) to optimal medical therapy alone in patients with stable CAD, aiming to evaluate both clinical outcomes and cost-effectiveness [31,38]. A three-year follow-up of the FAME 2 trial revealed that PCI in patients with stable CAD significantly improved angina relief and quality of life, with the PCI group consistently reporting less severe angina at all follow-up points over the three years. Additionally, while initial costs were significantly higher for the PCI group ($9,944 vs. $4,440; p<0.001), the total costs between the groups equalized by the three-year mark ($16,792 vs. $16,737; p=0.94). The incremental cost-effectiveness ratio for PCI compared to medical therapy was $17,300 per quality-adjusted life-year at 2 years, decreasing to $1,600 per QALY at 3 years, making PCI a more economically favorable strategy over time [39].

The second Randomized Intervention Treatment of Angina trial (RITA-2) compared initial strategies of PCI with continued medical therapy in patients with angina, enabling the evaluation of long-term health outcomes [40]. The three-year follow-up of the RITA-2 trial revealed that alleviation of cardiac symptoms, such as breathlessness and angina, in patients who underwent coronary angioplasty significantly improved their perceived quality of life compared to those receiving continued medical therapy. At one year, 9.7% of patients who underwent PCI and 4.8% of medically treated patients achieved the maximum physical functioning score of 100, indicating no limitations across all 10 items [41].

Impact of Revascularization on Survival and Myocardial Infarction in CCS

The fundamental principle of revascularization is that by restoring coronary blood flow, the extent of myocardial ischemia is reduced, leading to relief of angina symptoms and a decreased risk of cardiovascular events. CABG, as shown in a systematic overview of evidence from RCTs [10], has demonstrated survival benefits compared to medical therapy alone, particularly in patients with multivessel disease, diabetes, or reduced left ventricular function. The benefit of PCI (over medical therapy alone) for "hard" outcomes in CCS has been a long-standing issue of debate with mainly negative results in stand-alone trials.

The COURAGE trial, which included 2,287 patients [4], was a landmark study that evaluated the role of PCI plus optimal medical therapy (OMT) versus OMT alone in patients without left main disease and normal ejection fraction. There was no difference in all-cause mortality in the PCI group compared with the OMT group (19% vs 18.5% respectively; HR: 1.05, 95% CI: 0.87-1.27, p=0.62), nor in MI (13.2% vs 12.3%, respectively; HR: 1.13, 95% CI: 0.89-1.43, p=0.33), during a 4.6-year follow-up. However, there are some limitations of the trial, including the lack of high-risk patients, the use of bare-metal stents instead of drug-eluting stents (DES) in 97.3% of patients, the rather short follow-up (median of 4.6 years), the lack of ischemia-guided PCI and the high crossover rate; 33% of patients in the OMT group underwent eventually PCI [42].

Another significant trial in the same era was the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D), which compared the effectiveness of CABG versus PCI, with the goal of determining which method offered better long-term outcomes in patients with both diabetes and CAD [43]. Among 2,368 patients, only CABG was associated with a decrease in major cardiovascular events compared to medical therapy alone. BARI-2D shares similar limitations with the COURAGE trial (5-year follow up, DES in 34.7% of patients and 39% crossover rate).

The Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial investigated the outcomes of CABG versus PCI with drug-eluting stents in patients with diabetes and multivessel CAD [44]. The study demonstrated that CABG was superior to PCI in reducing the incidence of primary outcome (death, MI or stroke) at 5 years (18.7 vs 26.6%, p=0.005).

The FAME 2 trial studied patients with stable CAD and functionally significant stenosis, and demonstrated that FFR-guided PCI in addition to OMT reduced the need for urgent revascularization compared to OMT alone [31]. During a 5-year follow-up, there was a notable reduction in MI (overall and spontaneous [i.e. type 1]) among patients who underwent PCI, with a relative risk

reduction of 34% (HR: 0.66, 95% CI: 0.43-1.00) and 38% (HR: 0.62, 95% CI: 0.39-0.99), respectively [45].

The ISCHEMIA trial was a major clinical study designed to compare the outcomes of an invasive approach (catheterization with a view to PCI or CABG) versus a conservative approach (medical therapy without catheterization) for patients with stable CAD and moderate to severe ischemia (patients with left main disease and low EF<35% were excluded) [5]. The median follow-up was 3.2 years and the primary outcome was a composite of death from cardiovascular causes, MI, hospitalization for unstable angina or heart failure or resuscitated cardiac arrest. At 6-month follow-up, the primary endpoint was 5.3% in the invasive group and 3.4% in the conservative strategy group (Δ=1.9, 95% CI: 0.8-3.0) and at 4 years was 13.3% and 15.5%, respectively (Δ= −2.2, 95% CI= −4.4 to 0.0; adjusted HR: 0.93, p=0.34) [5]. In this trial, type 1 MI (spontaneous MI), which increases the risk of cardiovascular death [46], was more frequent in the conservative group, while procedural MI rates were increased in patients who followed the invasive strategy [47].

Lately, the results of the ISCHEMIA-EXTEND were presented including the extended follow-up (median seven years) of the patients who participated in the ISCHEMIA trial [48]. There was a 22% lower hazard of cardiovascular mortality in patients with an initial invasive strategy compared with those receiving OMT only (6.4% vs 4.4%, 95% CI: 0.63-0.96) and a lower risk of cardiovascular mortality after revascularization in those with multivessel disease (≥70% stenosis on computed tomography coronary angiography; hazard ratio [HR]: 0.68, 95% CI: 0.63-0.96) [18].

Observational studies also show consistent lower mortality or MI with revascularization in the long-term (10 years) especially in those with severe disease. Bainey, et al. have shown that an invasive strategy in patients with CCS and high-risk coronary anatomy relates to improved outcomes [49]. Rozanski, et al. have related early revascularization with decreased mortality among patients with normal left ventricular function and severe inducible ischemia as well as in patients with low EF and moderate or severe ischemia [50].

A recent meta-analysis of 25 RCTs, which included 19,806 patients, showed that revascularization provided a significant benefit for "hard" outcomes during longer follow-up [19]. Cardiac mortality was significantly lower in those who underwent PCI (relative risk: 0.79, 95% confidence interval: 0.67-0.93, p<0.01) and the risk of cardiac death was decreased by 19% for each four-year follow-up. Spontaneous MIs were also reduced after revascularization (relative risk: 0.74, 95% CI: 0.64-0.86, p<0.01).

In conclusion, evaluating the effect of revascularization on survival and myocardial infarction which represent events with rather low frequency in CCS requires large population samples and extended follow-up periods in order to achieve statistical significance for observed differences.

Benefit in patient subgroups

Numerous studies have focused on specific subgroups of patients with CCS (Figure 1), yielding several noteworthy outcomes. Categories of interest that will be discussed include patients with complex CAD, such as multivessel or left main disease, and those with left ventricular dysfunction. Additionally, asymptomatic patients with significant CAD represent another population of interest in terms of management.

Complex CAD

The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial evaluated the outcomes of PCI with drug-eluting stents (DES) compared to CABG in patients with three-vessel or left main disease [3]. The five-year follow-up of the SYNTAX trial highlighted that among a population of 1,800 patients, both CABG and DES-PCI provided significant and sustained quality-of-life improvements in patients with left main CAD over the study period. These improvements included a reduction in the number of angina episodes that occurred on a given day, and in the number of antianginal medications prescribed on that day. The analysis also revealed a significant interaction between angiographic complexity, as measured by the SYNTAX score, and angina relief. The mean difference in the SAQ score for CABG versus PCI was −0.9, 3.3, and 3.9 points for patients with low, intermediate, and high SYNTAX scores, respectively (p = 0.048 for interaction). This finding further supports the strong recommendation to prioritize CABG for patients with higher angiographic complexity [51]. Lastly, a 10-year follow-up of the SYNTAX trial revealed no significant difference in all-cause mortality between DES-PCI and CABG. At 10 years, 248 patients (28%) had died following PCI compared to 212 patients (24%) after CABG (hazard ratio [HR]: 1.19, 95% CI: 0.99–1.43, p=0.066). However, CABG demonstrated a clear survival benefit in patients

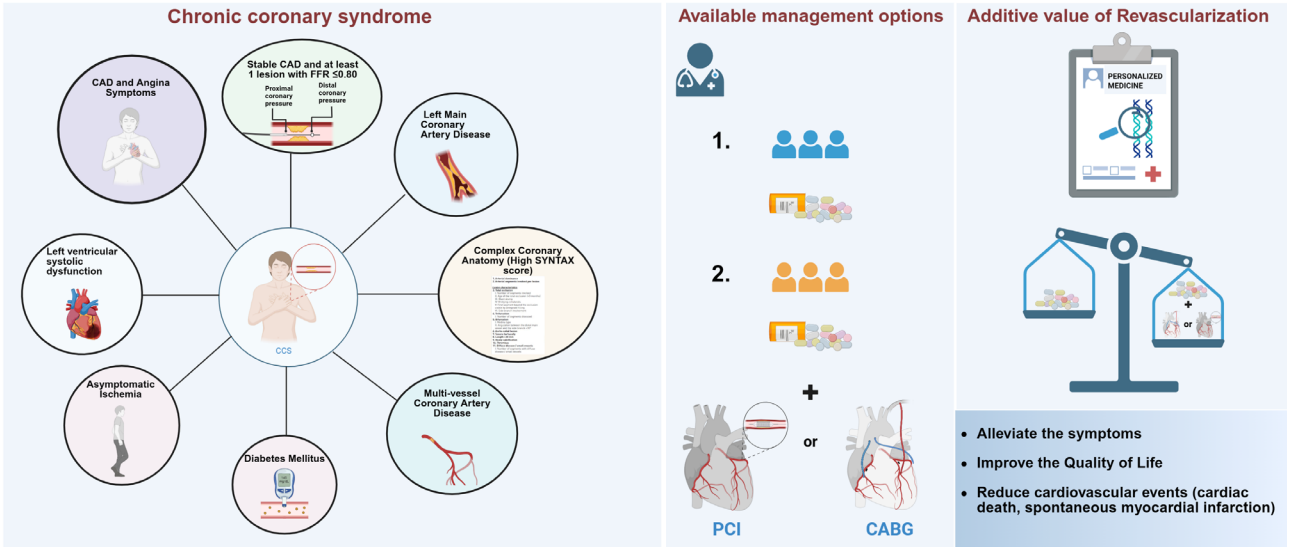

Figure 1. Management of patients with chronic coronary syndrome and the incremental value of revascularization.

Left panel: Overview of typical presentation and important subgroups of patients diagnosed with chronic coronary syndrome (CCS). *Middle panel:* This panel illustrates the available therapeutic options for CCS management, i.e. optimal medical therapy alone or optimal medical therapy in combination with coronary revascularization (either by percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). *Right panel:* The additive clinical value of revascularization strategies (PCI or CABG) beyond optimal medical therapy is highlighted. Emphasis is placed on personalized medical care according to which revascularization decisions should be individualized based on patient symptoms, coronary anatomy complexity, surgical risk, and disease severity. Benefits of revascularization include symptom relief, enhanced quality of life, and potential reductions in major cardiovascular events, notably spontaneous myocardial infarction and cardiac death.

with three-vessel disease (HR: 1.42, 95% CI: 1.11-1.81) but not in those with left main disease. In the subgroup of patients with left main disease, mortality rates were 27% for DES-PCI and 28% for CABG (HR: 0.92, 95% CI: 0.69–1.22 [52]**.**

In a registry investigating angiographic disease, Bainey et al. demonstrated that revascularization in patients with stable ischemic heart disease and high-risk coronary anatomy, defined as 3-vessel disease with ≥70% stenosis in all three epicardial vessels or left main disease with ≥50% stenosis (isolated or in combination with other lesions), was associated with improved long-term outcomes compared to conservative therapy [49]. The study followed a cohort of 9,016 patients with stable CAD and high-risk coronary anatomy between April 2002 and March 2016, and compared the primary composite outcome of all-cause mortality or MI between patients treated with revascularization and those managed conservatively. Coronary revascularization resulted in better outcomes compared to conservative management (inverse probability weighted hazard ratio [IPW-HR]: 0.62, 95% CI: 0.58–0.66, p<0.001).

In a prespecified secondary analysis of the ISCHEMIA trial, among patients with severe CAD (i.e. Duke score=6 corresponding to 3-vessel severe stenosis [≥70%] or 2-vessel severe stenosis with proximal LAD, N=659) according to the modified Duke Prognostic Index which categorizes CAD according to extent, location, and stenosis severity, the composite of cardiovascular death or MI was reduced in the invasive compared to the conservative arm at 4 years (11.6 vs 17.9%; difference: −6.3 [95% CI: −12.4 to −0.2]); this benefit was mainly due to a reduction in the rate of spontaneous MI in the invasive arm (5.4 vs 10.2%; difference: −4.8 [95% CI: −9.3 to −0.3]) [23].

The above observations underscore the importance of considering the coronary anatomical profile when determining treatment strategies for patients with stable CAD.

Left ventricular dysfunction

While revascularization has demonstrated clear benefits in CCS patients with complex disease, the outcomes in studies focusing on patients with left ventricular dysfunction have been inconsistent.

A secondary analysis from the ISCHEMIA trial, fo-

cusing on patients with heart failure or left ventricular dysfunction (i.e. EF 35-45% considering that EF<35% was an exclusion criterion for the trial), demonstrated that those randomized to the invasive strategy had a lower rate of the primary outcome (i.e., the composite of death from cardiovascular causes, MI, hospitalization for unstable angina or heart failure or resuscitated cardiac arrest) compared to the conservative strategy (17.2% vs. 29.3% at 4 years; difference: −12.1%, 95% CI: −22.6% to −1.6%), whereas no such benefit was observed in participants without heart failure/left ventricular dysfunction (13.0% vs. 14.6%; 4-year event rate difference: −1.6%, 95% CI: −3.8% to 0.7%). According to these outcomes, in the small, high-risk subgroup with heart failure or moderately reduced left ventricular EF, an initial invasive approach was associated with improved event-free survival [53].

Rozanski et al. prospectively studied a population of 43,443 patients to evaluate the association between stress-induced myocardial ischemia assessed by single-photon emission computed tomography (SPECT), revascularization (including PCI or CABG) within 90 days after SPECT, and all-cause mortality according to left ventricular EF. Among 3,560 patients with reduced EF (<45%), revascularization conferred no mortality advantage in cases of no or mild ischemia but demonstrated a significant mortality reduction when there was moderate (10-14%; HR: 0.67, 95% CI: 0.49–0.91) and severe (>15%; HR: 0.55, 95% CI: 0.38-0.80) ischemia. The overall findings indicated that early myocardial revascularization significantly reduced mortality in patients with severe inducible ischemia and normal left ventricular EF, as well as in those with low LVEF and moderate or severe inducible ischemia [50].

The Surgical Treatment for Ischemic Heart Failure (STICH) trial was designed to evaluate whether the combination of CABG and guideline-directed medical therapy for CAD, heart failure, and severe left ventricular dysfunction (EF<35%) would provide a survival benefit compared to medical therapy alone, and randomized 1,212 patients [29]. Although there was no significant difference in survival at a median follow-up of approximately five years (death from any cause: 36% in the CABG group versus 41% in the medical therapy group, HR 0.86, 95% CI: 0.72-1.04, p=0.12) [29], the extended ten-year follow-up showed benefit with CABG (all-cause mortality: 58.9% in the CABG group versus 66.1% in the medical-therapy group; HR 0.84, 95% CI: 0.73-0.97, p=0.02) [54]. Cardiovascular mortality (40.5% vs. 49.3%; HR 0.79, 95% CI: 0.66–0.93, p=0.006) and the composite of all-cause mortality or cardiovascular hospitalization (76.6% vs. 87.0%; HR 0.72; 95% CI: 0.64–0.82; p<0.001) were also reduced with CABG. These findings support the conclusion that, in patients with ischemic cardiomyopathy, CABG combined with medical therapy is associated with significantly lower 10-year rates of all-cause mortality, cardiovascular mortality, and the composite of all-cause mortality or cardiovascular hospitalization compared to medical therapy alone.

Lately, the REVIVED-BCIS2 trial randomized 700 patients with severe ischemic left ventricular systolic dysfunction and extensive CAD to medical therapy alone or revascularization by PCI [15]. In this trial, ischemic left ventricular dysfunction was defined as EF≤35%, extensive CAD was assessed with a British Cardiovascular Intervention Society jeopardy score of ≥6 (on a scale from 0 to 12, with higher scores indicating greater extent of disease), and demonstrable viability was required in at least four dysfunctional myocardial segments amenable to revascularization with PCI. Patients were also excluded if they had experienced an acute MI within four weeks prior to randomization, or if they had acute decompensated heart failure or sustained ventricular arrhythmias within 72 hours before randomization. At a medium-term follow-up of about 3.5 years, the primary endpoint of death from any cause or hospitalization for heart failure occurred in 129 patients (37.2%) in the PCI group and 134 patients (38.0%) in the optimal-medical-therapy group, with a hazard ratio of 0.99 (95% CI: 0.78-1.27, p=0.96). However, the Kansas City Cardiomyopathy Questionnaire overall summary score (range 0 to 100, with higher scores indicating better quality of life) appeared to favor the PCI group at both 6 and 12 months, with mean differences of 6.5 points (95% CI, 3.5 to 9.5) and 4.5 points (95% CI, 1.4 to 7.7), respectively.

The STICH and REVIVED trials exhibited several key differences that are worth highlighting [55]. Firstly, the available follow-up duration in REVIVED-BCIS2 was significantly shorter (3.5 years) compared to the ten-year extended follow-up in STICHES. Moreover, the available optimal medical therapy during the REVIVED trial period (2013–2020) was notably superior to that of the STICH recruitment period (2002-2007) since several important pharmacologic agents—such as angiotensin-receptor blockers (±neprilysin inhibitors), mineralocorticoid receptor antagonists and sodium-glucose co-transporter-2 inhibitors—were incorporated into standard care well

after 2010. Lastly, the use of implantable cardio-defibrillators and devices for cardiac resynchronization therapy, which are a critical part of current patient management in order to improve outcomes, was limited during the STICH trial period. Therefore, overall conservative patient management without revascularization was certainly further improved/optimized during the REVIVED period, thereby leading to superior outcomes compared to previous periods; this makes it harder to identify any incremental value of PCI on top of medical therapy. These differences may partly explain the discrepancies in the outcomes observed between the two studies.

Gaudino, M. et al. conducted a network meta-analysis that included all randomized controlled trials and observational studies comparing PCI, CABG, and medical therapy in patients with ischemic left ventricular systolic dysfunction [56]. The primary outcome assessed was mortality at the longest available follow-up; the analysis included 23 studies, with 23,633 patients, and 4 of the studies were randomized controlled trials. Compared to CABG, PCI was associated with higher mortality (IRR 1.32, 95% CI: 1.13–1.53), cardiac mortality (IRR 1.65, 95% CI: 1.18-2.33), MI rate (IRR 2.18, 95% CI: 1.70-2.80) and repeat revascularization rate (IRR 3.75, 95% CI: 2.89-4.85). Medical therapy also showed worse outcomes than CABG, with higher mortality (IRR 1.52, 95% CI: 1.26-1.84), cardiac mortality (IRR 3.83, 95% CI: 2.12-6.91), MI rate (IRR 3.22, 95% CI: 1.52-6.79), and revascularization rate (IRR 3.37, 95% CI: 1.67-6.79). Of note, PCI reduced cardiac death compared to medical therapy (IRR 0.43, 95% CI: 0.24-0.78), while CABG was the best strategy for reducing mortality, cardiac death, MI, and repeat revascularization. The authors concluded that CABG appears to represent the most effective therapeutic strategy for CAD with left ventricular dysfunction. However, this conclusion is predominantly derived from observational data. Rigorous randomized controlled trials comparing CABG and PCI in this patient population are warranted to provide definitive evidence.

Asymptomatic patients

Asymptomatic, i.e. "silent", ischemia is regarded as a marker of poor prognosis, particularly following MI [57]. However, in patients with stable CAD, the prognostic significance of asymptomatic ischemia and the benefits of revascularization remain less well established.

The Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) was a randomized, unblinded, controlled trial conducted in the 1990s at public hospitals in Switzerland. The study included 201 patients with recent MI (within the last three months) who had silent myocardial ischemia (ECG ischemic changes at exercise test) confirmed by stress imaging, and one or two vessel disease [58]. Over a mean follow-up of 10.2 years, the PCI group (without stenting during that era) had 27 major adverse cardiac events (defined as cardiac death, nonfatal MI, or symptom-driven revascularization) compared to 67 in the drug therapy group (adjusted HR: 0.33, 95% CI: 0.20–0.55; p<0.001), with an absolute event reduction of 6.3% per year (95% CI: 3.7%-8.9%; p<0.001). Ischemia rates (defined by ischemia on repeat exercise ECG) were lower in the PCI group at follow-up (11.6% vs. 28.9%; p=0.03), and EF remained stable (53.9% to 55.6%), while significantly declining in the medical therapy group (59.7% to 48.8%; p<0.001) during follow-up. The study concluded that among patients with a recent MI, silent myocardial ischemia confirmed through stress imaging, and one or two vessel disease, PCI was associated with a significant reduction in the long-term risk of major cardiac events compared to anti-ischemic drug therapy [58].

The FAME 2 trial enrolled 888 patients with at least one hemodynamically significant stenosis (FFR <0.80) in a major epicardial artery who were randomized to receive either optimal medical therapy alone or PCI in addition to medical therapy (PCI group) [31,38,45]. Of these, 98 patients were asymptomatic with 53 assigned to PCI plus medical therapy and 45 to medical therapy alone. Patients randomized to PCI had a significantly lower rate of death/MI (9.4% vs. 31.1%, HR: 0.24, 95% CI: 0.08-0.66, p=0.006). This post hoc analysis highlights that PCI is associated with superior outcomes compared to medical therapy alone in stable patients with silent ischemia [59].

DISCUSSION

The perfect balance between optimal medical therapy alone or adjunctive revascularization (either with PCI or CABG) in the management of CCS remains intricate. The objective of the revascularization strategies is not only to alleviate symptoms but also to improve quality of life and long-term cardiovascular outcomes (Figure 1).

CABG, especially in patients with complex anatomy, such as multivessel disease, presents durable benefits in alleviating symptoms. The ISCHEMIA and the FAME-2 follow-up data demonstrated that in patients with symptoms, revascularization with PCI enhances quality of life and diminishes angina symptoms in patients

with moderate to severe ischemia according to SAQ scores [5,39]. The ORBITA-2 study provided further insights into the role of PCI in stable angina. The outcomes demonstrated that PCI resulted in significantly lower angina symptom scores at 12 weeks compared to placebo [7]. PCI provides meaningful improvement in symptom relief and health status, particularly in patients presenting ischemia symptoms that do not receive medical treatment.

CABG has been proven to provide a long-term survival benefit in patients with complex disease or reduced LVEF, as shown by landmark studies such as SYNTAX and STICH [3,60]. It is the preferred strategy for decreasing mortality and MACEs in these high-risk cohorts. The STICH trial and its long-term follow-up also underlines the importance of CABG in reducing hospitalizations in patients with ischemic cardiomyopathy.

The added benefit of PCI regarding cardiovascular mortality and myocardial infarction remains unclear although meta-analytic data including very large patient numbers and very long follow-up indicate potential advantages with percutaneous revascularization. It becomes evident that the prognosis of CCS, especially with the increasing number of medications with highly positive outcomes during the last two decades, is rather benign with low event rates for hard outcomes. Thus, it is even harder to demonstrate an additional gain by PCI; this requires population sizes which are infrequently included in single randomized trials. Furthermore, sub-analyses focusing on cardiac outcomes, i.e. cardiac mortality and spontaneous type 1 MI, instead of broad unfocused endpoints such as all-cause mortality, support the value of PCI. Lastly, PCI seems to be particularly beneficial in certain patient populations with more severe disease, and it is also a good alternative for patients with high surgical risk, thereby highlighting the importance of individualized patient care and appropriate patient selection.

CONCLUSION

CCS is a lifelong disease with high prevalence worldwide. Optimal medical therapy is the foundation of treatment in all patients with CAD and physicians should strictly adhere to the guidelines for best management practices. Revascularization is not the first choice for all patients, but it offers significant benefits. CABG has been associated with improved long-term survival. Although the benefit of percutaneous revascularization for the management of CCS has been questioned during the last two decades, there is now a large amount of clinical evidence to make strong inferences for the value of PCI in preventing cardiac-specific events. The final decision for patient management should be based on the operator's expertise, the patient profile and the patient's choice. Future research should focus on the long-term outcomes of revascularization and the development of a more personalized treatment strategy to provide optimal care in CCS patients.

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