



A Comprehensive Review on Cardiovascular Disease Detection, Risk Assessment, and Treatment Using A Network Pharmacology Model

Vijay Kumar Jaiswal ^{1*}, Monika Barsagade ¹, Jitendra Sinha ¹

Abstract

Introducing a new healthcare service based on study findings can be challenging. This review presents the outcomes of a pilot project implemented in Belgian neighborhood pharmacies, assessing the risk of diabetes and cardiovascular diseases. The service deployment followed an integrated approach using the RE-AIM (Reach Efficiency Acceptance Implantation Management) framework. The study highlights the development of a network of medications influencing cyclic guanosine monophosphate (cGMP), potentially causative for various cardiac diseases. It discusses the limited efficacy and crucial factors affecting optimal execution. It suggests exploring additional approaches like interprofessional seminars, a data-sharing system, and outreach efforts to enhance awareness of pharmacists' expanded roles. While the service is simple and practical, ensuring its effectiveness, sustainability, and broader adoption requires financial and external support.

Significance | Contribution to advancing diagnostic methods, proposing innovative treatment approaches, and demonstrating the effectiveness of pharmacist-led preventive strategies for improving population health.

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1. Introduction

Noncommunicable Diseases (NCDs) are chronic and protracted illnesses arising from genetic, ecological, psychological, and behavioral variables Lane et al. (2021). The cost is well recognized and significantly influences the quality of living. To mitigate the effects of diabetes and cardiovascular illnesses, it is necessary to adopt personal and communal strategies that prioritize the reduction of modifiable risks related to these conditions and their consequences. Establishing a cost-effective method for preventing and controlling these illnesses is imperative Wu et al. (2019). Preventive approaches, such as timely identification and assistance, have proven economically beneficial expenditures. Early provision of these interventions can effectively impede the advancement of the disease and the occurrence of complications, thereby diminishing the necessity for costly treatments. Healthcare practitioners are crucial in addressing the financial burden of NCDs Bi et al. (2021).

The growing responsibility placed on healthcare practitioners to oversee population wellness and associated expenses necessitates that health systems explore novel approaches to optimize resource allocation Hartleb et al. (2022). These initiatives encompass the provision of preventative services. The local pharmacists are in an advantageous position. They frequently serve as the initial interface between people and the healthcare system, thanks to their easy accessibility, longer operating hours, and ability to

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provide pharmacological treatment without requiring a scheduled visit.

In recent times, the function of pharmacists has gradually evolved from just distributing medications to being providers of assistance and knowledge, with a particular focus on promoting the optimal utilization of medicines Gong et al. (2023). An increasing area of study has been on pharmacist-led screening methods, which can significantly enhance public health. Multiple studies have shown that general pharmacy screening is possible and successful in identifying previously undiagnosed diabetes and cardiovascular illnesses Hill-Briggs et al. (2021) Nielsen et al. (2021).

Over many years, there has been a decrease in the number of pharmaceuticals that have been given approval, which suggests that there are underlying issues related to the effectiveness and creativity in fundamental, translated, and industrial studies Zhang et al. (2019). Possible factors for this phenomenon include, among other things, the whole notion of illness, which primarily relies on symptoms, a structure, and its observable function instead of on biological processes. A comprehensive knowledge of the causes and mechanisms of illnesses is still uncommon, and it is mainly applicable to diseases caused by a single gene mutation Ding et al. (2019). Common and complicated diseases are predominantly managed by addressing the signs, risk factors, or indicators. However, this method is characterized by low accuracy, as indicated by the vast numbers required for therapy and the limited effectiveness of existing medications Zheng et al. (2024). Cardiology is not exempt from this phenomenon, and due to its numerous unresolved requirements, it constitutes one of the most significant areas of lacking knowledge in the field of medicine Jin et al. (2021).

Therapeutic actors that manipulate the subsequent messaging cyclic guanosine monophosphate (cGMP) appear to be a solution to this theoretical obstacle and have the potential to pave the way for a novel, mechanism-based method for treating various diseases, utilizing the capabilities of big data, relationships, and systems healthcare Wang et al. (2023) Subramanya et al. (2021). cGMP regulators are establishing themselves as highly intriguing molecules in current cardiovascular medication research. This might be because these treatments address signs and target the underlying illness process in a specific group of patients instead of simply relieving symptoms or modifying risk variables Petrain et al. (2022).

So, the evolving role of pharmacists, the challenges in pharmaceutical studies, and the potential of cGMP regulators signify a shift towards more personalized and mechanism-based approaches in the treatment of cardiovascular diseases and other health issues.

2. Literature review and Analysis

This section examines several proposed approaches to diagnosing cardiovascular disease and its associated obstacles. This analysis aids in the development of more effective methodologies in the future.

The research introduces CardioXNet, an innovative and efficient end-to-end Recurrent Neural Network (RNN) design designed to accurately identify five categories of cardiac examination: typical aorta stenosis, mitral narrowing, mitral regurgitation, and mitral valve collapse. This is achieved by analyzing the raw signal Shuvo et al. (2021). The automation of the procedure has been achieved by incorporating two distinct learning stages: representations learning and sequencing residual training.

This study will be specially designed around a particular database that will mainly consist of the diagnostic data of individuals who have previously been identified with potential cardiac disease. An innovative, intelligent method is suggested to identify cardiac illness Nawaz et al. (2021). The proposed intelligent system classifies heart illness based on its symptoms as either Positive or Negative.

This research presents the development of an ensemble model that combines Long Shorter-Term Memory (LSTM) and Generative Adversarial Networks (GAN). The results show that this ensemble model outperforms the individual Deep Learning (DL) model employed in this paper Rath et al. (2021). The GAN architecture is chosen to disclose unbalanced information by creating and using supplementary information for identification. The suggested optimal detection approach can be extended to handle more illnesses and medical problems.

This article examines the utilization of zebrafish, scientifically known as *Danio rerio*, as a model organism for investigating circulatory development and illness Bowley et al. (2022). The research outlines the utilization of zebrafish prototypes to investigate the underlying processes that underlie cardiac conditions such as congenital heart problems, cardiomyopathy, conduction illnesses, and regeneration, as well as vascular diseases including dysfunctional endothelial cells and atherosclerosis, metabolism of lipids, vascular aging, neurovascular physiology, and strokes Vinothkanna et al. (2023).

The research offers a description of the methods and origins of omics data, presents an overview of the network concept, and showcases examples of innovative methods that integrate gene regulating and co-expression systems, metabolism, and phenomics with information systems methods to gain fresh insights into heart illness Joshi et al. (2021). Utilizing systems methods will be essential for integrating data from several omic techniques.

The research provides a concise overview of the epigenetic background and crucial regulatory processes involved in heart disease Shi et al. (2022). The research presents (1) the historical background and fundamental principles of epigenetics, (2) the

regulatory processes of epigenetics in cardiovascular illness, and (3) the prospective use of epigenetics as a therapeutic method for treating heart failure. The research examines the experimental investigations and medications targeting these crucial epigenetic enzymes for treating cardiovascular disorders.

The research discussed the pharmacology and toxicity of synthesized organoselenium chemicals and several naturally generated amino acids Nogueira et al. (2021). Selenium has been utilized as a significant instrument in synthetic biology and as a medicinal agent since the mid-19th to early 20th century. The results of the clinical studies investigating the efficacy of ebselen as a lithium mimic or protease metalloproteinase will have significant implications for the production of organoselenium chemicals Lagunin et al. (2020).

This study comprehensively synthesized the most recent advancements in understanding the processes behind ferroptosis Zhang et al. (2022). The research analyzes the impact of iron metabolism on cardiovascular disorders. The study evaluates the treatment strategies to address ferroptosis in cardiovascular disorders.

This section provides a concise summary of the articles about cardiovascular disease and the methods used for its diagnosis. The presence of problems and concerns in current methodologies highlights the necessity for a new approach to identifying cardiovascular illnesses, utilizing a network pharmacology model.

3. Proposed Cardiovascular disease detection using a network pharmacology model

This section examines the techniques for identifying cardiovascular illness using the network pharmacology model. This technique discusses the study area, samples, experiment specifics, and the assessment of risks associated with the topics.

3.1 Study Design

Retrospective and observational research was done to assess the operation of the screening services. Following the Reach Efficiency Acceptance Implantation Management (RE-AIM) paradigm, the study utilized an integrated approach, including quantitative and qualitative evaluation. This implementation paradigm is quite prevalent in public wellness and medical treatments for planning and assessment. The model consists of five measurements: reach (R), efficiency (E), acceptance (A), implantation (I), and management (M). The gathered results were carefully determined to accurately depict the RE-AIM characteristics and investigate the potential obstacles and enablers of these measurements while also tailored to a pilot project's specific environment and goals.

3.2 Participants

Patients who expressed a desire to participate in the screenings were requested to provide their agreement for utilizing their data in scientific evaluation. They had to agree to grant permission for

the college investigators to contact them for a brief conversation on their involvement. Every pharmacist who took part in the research effort was qualified to participate in the research.

3.3. Network Pharmacology Model

GMPopathies result from various dysfunctions in GMP's production, degradation, or signaling. Nevertheless, networking medicine research demonstrates that the particular cGMP source is significant. The Network Pharmacology Model (NPI) networks of confirmed seed genes indicate that cGMP signaling is organized into several modules. Therefore, the analogs might not effectively replace the role of GC-1/2 in case of loss. sGC boosters do not effectively replace GC-A or GC-B's function in producing cGMP. This phenomenon is demonstrated in artificial cardiac failure.

A complicated disease process is constituted by a network of proteins instead of being characterized by a single target molecule. The precise origin of cGMP inside these network components is significant since they cannot be substituted for one another. A further substantial treatment alternative arises from this, namely network pharmacology. Malfunctioning multi-protein networks can be restored to a more normal condition using multiple medicines targeting distinct proteins within the same component. This should happen synergistically, enabling decreases in the dosage of each particular medication while maintaining overall effectiveness and decreasing adverse effects. This technique, known as mechanism-based networking pharmaceuticals, should be distinct from classical combination treatment. In traditional combination treatment, medications with different mechanisms of action are put together, none of which directly causes the disease, and the outcomes are maximally cumulative. An example of how this technique is used in practice is by combining three pharmaceuticals to treat individuals with cystic fibrosis. These treatments specifically target a malfunction in the body's mechanisms that cause the disease, making them suitable for up to 90% of cystic fibrosis sufferers.

Due to the presence of cardiovascular signs or characteristics, cystic fibrosis serves as a suitable paradigm for both network pharmaceuticals and an organ-agnostic strategy for treating illness. Regarding cGMPopathies, a potential plan is to increase cGMP synthesis while blocking cGMP breakdown. However, it is crucial to select these combinations according to solid data and precisely within a specific disease component (Fig. 1).

Preclinical studies suggest phosphodiesterase (PDE) has a more significant role in controlling GC-1/2 signaling, particularly in erection problems. PDE9 and PDE2 are more inclined towards signaling, particularly in coronary artery disease. It is yet to be determined if specific clinical trials with poor results (such as those involving cinaciguat and tadalafil in heart failure) are clarified using a less-than-ideal cGMP-modulating treatment.

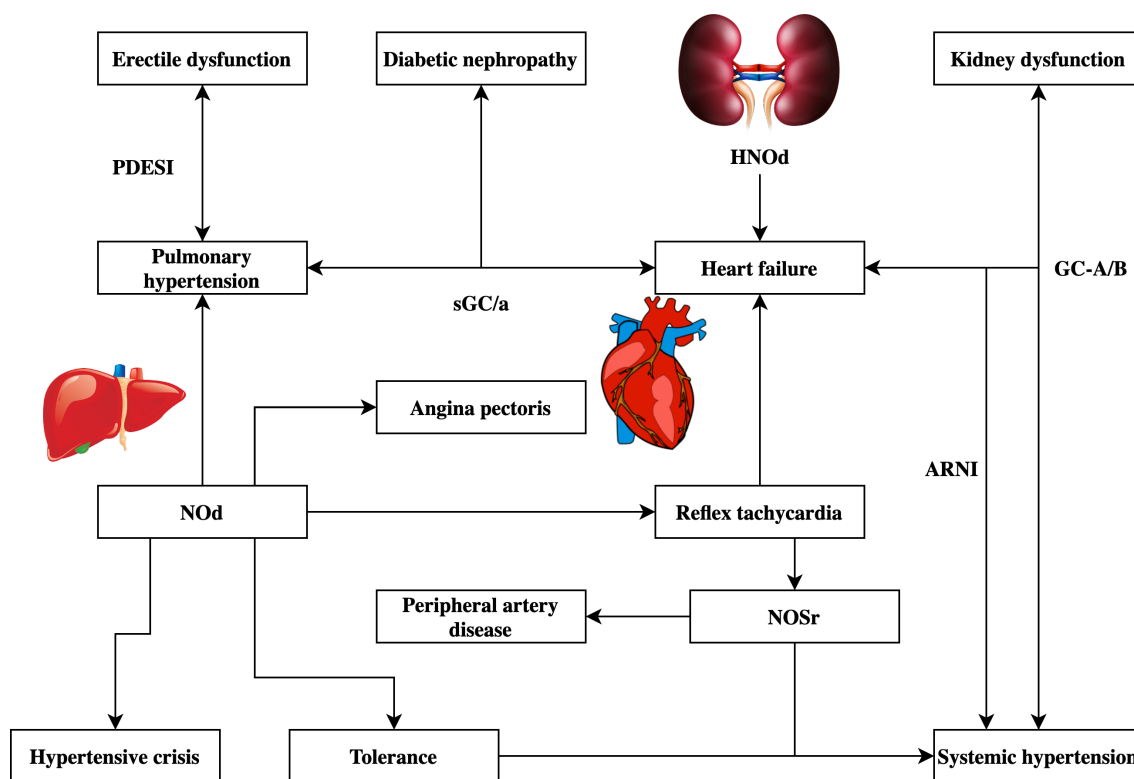


Figure 1. cGMPopathies and evidence-related treatment

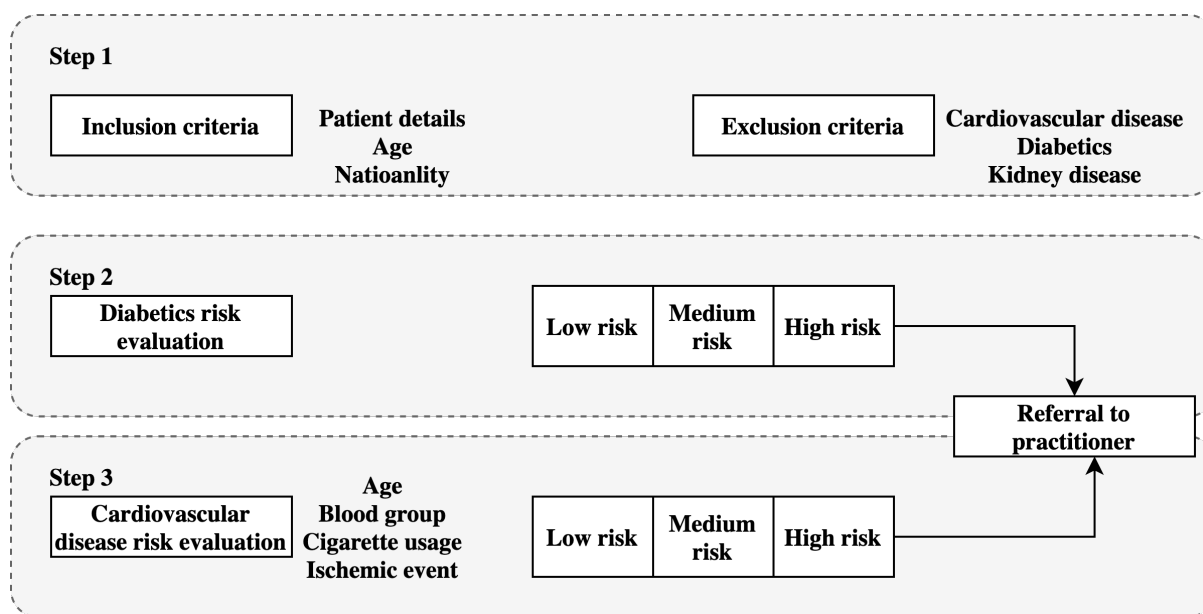


Figure 2. Screening process of the proposed method

Some pairings could be more suitable in one situation and ideal in another. An instance of this is seen with the combination of tadalafil and NO supporters, which is prohibited due to its propensity to cause severe hypotension.

The study reported a comparable significant reduction in systemic arterial pressure in individuals with pulmonary hypertension when treated with riociguat and tadalafil. The preliminary clinical research with a limited sample size of six patients examined the effects of combining the well-established organic nitrates and the phosphodiesterase-5 inhibitors (PDE5), tadalafil. This combination results in improved management of arterial pressure in individuals suffering from 'resistant' hypertension. Another demonstration of the notion was provided by the second stage of the study of neprilysin reduction in patients with Pulmonary Arterial Hypertension (PAH) who were previously stable on PDE5. This combined set of mechanisms offers an extra advantage in treating PAH.

3.4 Description of the Screening Test

Between January 2022 and December 2023, a group of pharmacies in Brussels offered patients the chance to participate in random testing for hazards related to diabetes and heart disease. They explicitly stated that this novel service was included in an analysis to assess its viability in community pharmacies using quantitative and qualitative methods.

The screening process adhered to a sequential approach, as depicted in Fig. 2. Initially, the pharmacist evaluated the patient's suitability by considering the criteria for being included or excluded. The test first assessed the patient's potential for diabetes and then set their risk for cardiovascular illnesses. The decision to seek advice from an ordinary doctor or expert was made based on the risk evaluation results. Only those aged between 40 and 65 who reside in Brussels were qualified. The examination was provided at no cost to provide accessibility for the most disadvantaged and socially deprived persons. To eliminate patients who had been identified with the specific diseases of interest, those under regular medical supervision by a primary care physician or receiving treatment for diabetes, cardiovascular illnesses, or renal disorders were not included in the study.

The first assessment relied on the translation of the Finnish Diabetes Risk Scoring survey, a standardized tool used to identify persons with a high likelihood of acquiring type 2 diabetes mellitus during a 10-year timeframe. The survey is a dependable, helpful, and user-friendly screening instrument endorsed by healthcare standards and assessment. The questionnaire has eight inquiries about the participants' biographical attributes, healthcare background, and lifecycle habits. Participants who scored above seven were encouraged to undergo hemoglobin A1C measurement using a screening gadget for risk profiling.

The cardiovascular assessment was conducted using the Boland method. The assessment was based on the individual's medical background and tests of their arterial pressure. The six risk variables that were taken into account are as follows: age [A], arterial pressure [B], tobacco use [C], diabetes [D], an individual ischemic event [E], and a family ischaemic action [F]. Participants having a prior medical history of diseases were excluded from eligibility. Therefore, only the remaining four criteria were evaluated. If the participant exhibited any of the 4 risk variables and did not solely exhibit the threat associated with smoking, their cardiovascular risk assessment was conducted using the validated database. This estimating tool utilizes age, gender, overall fat levels, and smoking habits to determine the 12-year probability of experiencing fatal cardiovascular illnesses. It was proven appropriate, reliable, and exact for evaluating coronary artery disease in Belgium. As this study did not assess the total cholesterol value, the average cholesterol reading for men and women in Belgium was utilized to determine the participants' ratings. Participants were classified as having low to medium cardiovascular danger if they met one of the following criteria: they possessed no risk variables (ABCF-), their cardiovascular hazard was solely attributed to smoking (C+), or outcomes were less than 4%. Participants were classified as having an elevated cardiovascular danger if their score fell between 4 and 10% and were classified as having a high cardiovascular threat if their score was 11% or above.

The pharmacist offered counseling and personalized guidance for individuals with lower and medium-risk assessments to assist in managing the identified risk parameters. Participants who have a score between 6 and 12 and an HbA1c studying of $\geq 5.8\%$, a risk assessment score of ≥ 10 and an HbA1c studying $\geq 6.2\%$, or a heart disease score of ≥ 12 , or a heart disease score of 5 to 10 with higher blood stress or a circumference of ≥ 85 cm for female and ≥ 95 cm for boy, are classified as a higher threat. Those individuals are referred to a physician for additional testing.

3.5 Data Analysis

The discussions were captured in audio format and translated word for word. The transcriptions of pharmacists and individuals were coded independently. Two investigators used the Nvivo program to code the first three recordings deductively. The rules were contrasted and aligned, and any inconsistencies were addressed through discussion. The rules were categorized into themes and organized based on the aspects investigated. The recordings provided were encoded using the predetermined coding hierarchy. After every three assessments, any inconsistencies in encoding were addressed, and more rules were incorporated into the coding hierarchy. The quantitative information collected from individuals who agreed to the data investigation was analyzed descriptively using Excel.

This section explores the methods of detecting cardiovascular diseases by applying the network pharmacology model. This approach examines the geographical region under research, the collected samples, the precise details of the experiment, and the evaluation of the potential hazards related to the subjects.

4. Experimental Outcomes

The evaluation service was conducted in two successive phases, with overlapped dates: from January 2022 to December 2023. The stages were conducted with 25 pharmacists and 20 pharmacies, with five pharmacies participating in both locations. To assess the execution of the service, a comprehensive set of 25 semi-structured discussions was carried out for individuals who participated in the evaluation session. Four discussion groups, including a collective of 18 pharmacies, were arranged via Zoom. Three telephonic one-on-one conversations were carried out with pharmacists who could not participate in the focus groupings. Throughout this qualitative study, some significant themes that affected the execution of the evaluation services were found.

4.1 Reach

Thirty-two pharmacies recruited 500 individuals in the assessment process during the research. The average number of patients per pharmacist was 15, ranging from the lowest of one individual to a high of 40 individuals.

4.2 Patient Characteristics

Out of the 500 individuals, a majority 410 (82%) agreed to have their data analyzed for scientific reasons, including individuals aged 60 years and above (9%). By eliminating this latter category, 375 individuals were deemed acceptable for the according-to-protocol assessment. Most participants in the study were female, accounting for 60% of the total. Their ages varied from 25 to 65 years, with a mean of 55.

4.3 Risk Profiles

88% of the 330 individuals with a score of ≥ 6 were asked to undergo level testing. The observed values range was between 3% and 6.5%, with a median reading of 5.7%. The measurement was omitted for five individuals (1.4%), leading to an indeterminate risk assessment. Out of all participants, 150 (39%) with minimal risk characteristics and 155 (41%) with medium risk characteristics got counseling on managing their identified risk factors. Nevertheless, a total of 75 individuals (20%) were detected with diabetes and were recommended to a physician for additional assessment.

Out of the 300 individuals who had a minimal or moderate threat profile for diabetes, a total of 250 individuals (84%) took part in the assessment of cardiovascular illnesses. Out of them, 65 individuals (25.2%) were determined to have a minimal risk of cardiovascular diseases since they either had no clinical risks [ABCF-] or solely smoked cigarettes [C+]. The threat was also

evaluated utilising the calibration graph for the 180 individuals (69%) who exhibited additional risk variables [ABF+]. In summary, 220 individuals (87.4%) were determined to have a lower or medium threat assessment and got instructions on heart disease prevention. Nevertheless, six individuals with a score of ≥ 10 (2.5%) and twenty individuals (7.2%) with a score of 5 and 10 who exhibited elevated blood sugar levels or a waist circumference of ≥ 70 cm for females and ≥ 80 cm for male, were identified as being at a heightened threat and were assigned to a doctor for evaluation.

4.4 Outcome of Patients

The efficacy study was assessed just at the initial phase of the effort. Out of the 225 individuals examined, 50 individuals (24.2%) were identified as having an elevated risk for acquiring either diabetes or cardiovascular illnesses. Out of the total number of patients, 19 individuals declined to consent to contact, resulting in 35 potential participants for the efficacy assessment. Just 22 individuals were able to be reached.

Two individuals were unaware of their high-risk profile since they said the pharmacist did not transmit this information. Specific individuals gave precedence to alternative medical issues or delayed scheduling medical treatment until there had been a decline in the number of confirmed COVID-19 patients. 6 individuals who underwent risk evaluations were sent for further testing. Among these, five were found to be free of diabetes or cardiovascular disorders, while one had been identified with diabetes.

4.5 Patient Perception and Risk Assessment

Individuals exhibited a state of calmness during the operation. However, pharmacists noted that most individuals were reluctant to puncture their fingers and consistently sought help from the pharmacist. Individuals who did not require an HbA1c assessment said they would feel more confident in the accuracy of the lower threat group if they viewed the HbA1c outcomes. The participants strongly valued the pharmacists' interaction, finding it straightforward, comforting, and polite. The absence of a printed document was seen as a drawback since the absence of tangible data might prevent individuals from losing track of the intention and results of the test.

4.6 Sustainability Factors

The pharmacists expressed their desire to enhance their cooperation with other professions, particularly physicians, to sustain this form of preventive treatment. They believed that this would improve the monitoring of the sufferers. A proposal was made to implement this idea by organizing medico-pharmaceutical conferences to foster cooperation toward providing services. Patient results and measurement information might be exchanged via an electronic health system to facilitate this partnership. The procedure should be carried out with the

explicit agreement of the participants and ideally through a predetermined healthcare pathway. The majority of pharmacists believed that the training conducted before the start of operations was adequate. It was proposed that if preventive-related services were implemented regularly, training in such activities should be incorporated into the pharmacy master's program.

Participants and pharmacists expressed the need for a more comprehensive strategy for the knowledge initiative, as pharmacists had to dedicate significant effort to reach out to potential high-risk patients. Possible strategies discussed included community-based initiatives and the proposal for increased media exposure.

5. Conclusion and Future Study

Multiple medicines that modulate cGMP have been introduced into clinical practice, with recommendations for a broad range of cardiovascular illnesses. Genetic data suggests that addressing faulty cGMP signaling, known as cGMPopathies, can develop into a mechanism-based, causative treatment in cardiovascular therapy. Although all essential medications appear accessible, the primary obstacle will be to recognize individuals who have the appropriate indications and not only possess a proper physical manifestation but, more critically, have a malfunction in cGMP, known as the cyanotype.

Given the heightened burden on healthcare providers, pharmacists can assume a more proactive stance by diagnosing, counseling, and referring individuals with hitherto undetected ailments and helping individuals at risk to avoid advancing their disorders. The individual's favorable perception of the risk evaluation and the enthusiastic participation of the pharmacists are promising indicators for the long-term viability of pharmacist preventative activities. The neighborhood pharmacy was often seen as easily reachable and capable of reducing the risk assessment required. Simultaneously, the ease of managing the service showed its practicality in everyday implementation. It is advisable to consider implementing external assistance techniques such as interprofessional seminars, tailored software, a digital data-sharing system, supplementary training, and broad-based advertising campaigns. These initiatives enhance understanding of the pharmacy's evolving responsibilities, encourage the staff to embrace new services, and facilitate coordination with physicians to guarantee proper follow-up of patients recognized as high-risk. At political levels, discussions on financial incentives and compensation for pharmacies and expanding the regulatory structure for reimbursing point-of-care testing should occur. These factors will play a crucial role in ensuring the long-term viability and widespread adoption of risk-assessment assistance at a national scale. More research should assess the efficacy and oversee the execution of preventative services to develop

appropriate long-term strategies for overcoming obstacles at various phases of adoption.

Author contribution

P.G., R.P., U.J. wrote, reviewed and edited the article. All authors read and approved for publication.

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Competing financial interests

The authors have no conflict of interest.

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