NOVEL AFFORDABLE STRATEGY TO DIAGNOSE EARLY RENAL AND HEART FAILURE IN PATIENTS AFFECTED BY DIABETES MELLITUS AND HYPERTENSION

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BACKGROUND AND RATIONALE OF THE PROJECT: Kidney and Cardiovascular diseases are major causes of morbidity and mortality contributing a sizeable portion of the total disease burden worldwide (1). Since kidney's and heart's physiological functions are intimately linked, the same spectrum of diseases could damage both organs at one time, deeply modifying the treatment and the prognosis of the patient. Therefore, an early diagnosis is of paramount importance in order to identify and possibly alter the disease progression.

In a low-income setting such as Africa, where the high prevalence of kidney and cardiovascular diseases meets often limited resources (2) the finding of affordable and reliable screening tools is of cornerstone importance to target high risk patients who will benefit the most from medical treatment. This becomes extremely relevant in the outpatients setting, where the high regimen of patients often implies high amount of resources that not necessarily convey absolute clinical accuracy (3).

Therefore, we propose a new simple and cost-effective screening method based on physical examination, urine dipstick and ECG acquired via a portable smartphone based device. Of note, ECG plays a crucial role in the identification of patients at highest risk and represents the most cost-effective method to address large population screening campaigns (**4-6**).

The D-Heart Electrocardiograph has been developed for iOS and Android operative systems, enabling the acquisition of surface electrical signals through 5 electrodes (3 peripheral leads and 2 precordial (V2-V5) leads) connected to a portable hardware that streams via Bluetooth the trace to the smartphone (7).

The potential impact of such a technology, combined with accurate physical examination and urine dipstick, opens several promising perspectives for low-cost cardiovascular screening strategies pointing at the identification of high risk hypertensive and diabetic patients (**8**).

DESIGN AND MAIN OBJECTIVES: The present study is a prospective trial and main objectives are:

1. Early detection of renal and cardiac failure in patients with relevant risk factors (hypertension, DM) in order to establish medical interventions to prevent the progression to chronic kidney disease and end-stage renal and heart failure;

2. Creation of a simple and cost-effective cardiovascular screening method (including a clinical evaluation, urine dipstick and D-Heart ECG) applicable in the daily medical routine.

Secondary objectives are:

1. Systematic data collection of the incidence of patients with signs of early renal and cardiac impairment;

2. To establish the cultural response and the user friendliness of local health workers with respect to The D-Heart electrocardiograph.

METHODS: Each patient referred to the diabetes mellitus and/or hypertension outpatient clinic at Lacor Hospital will:

1. To answer basic anamnestic questions (see attachment 'Anamestic Sheet');
2. Undergo physical examination focusing on:
    - blood pressure mesaurment; ***Carried out following current ESC guidelines on BP assessment. Three BP measurement would be carried out by the PI during the visit and manual sphygmomanometer would be used. Mean systolic value would be categorized into 4 categories: 90<BP<130mmHg; 130<BP<150mmHg; 150<BP<170mmHg and 170<BP<200mmHg (3).***

    - Heart murmurs;
    - Lung auscultation;
    - Signs of Peripheral edema;

3. Undergo a routine ECG performed with D-Heart electrocardiograph;
4. receive a urine dipstick and glycemic level control (total blood glucose). ***The test method consists of immersing the test strip completely in a well mixed sample of urine for a short period of time, then extracting it from the container and supporting the edge of the strip over the mouth of the container to remove excess urine. The strip is then left to stand for the time necessary for the reactions to occur (usually 1 to 2 minutes), and finally the colours that appear are compared against the chromatic scale provided by the manufacturer. The test strips consist of a ribbon made of plastic or paper of about 5 millimeters wide, plastic strips have pads impregnated with chemicals that react with the compounds present in urine producing a characteristic colour. For the paper strips the reactants are absorbed directly onto the paper. Paper strips are often specific to a single reaction (e.g. pH***

measurement), while the strips with pads allow several determinations simultaneously (figure 1).

Figure 1. Schematic representation of Urine Dipstick Test.

Patients with a negative physical examination or normal BP readings and Glucose values may stop the screening at this point, while those with urinary dipstick alterations will go on with creatinine measurement.

The data would be available only to the researchers and stored in a protected database.
Each ECG would be either stored in the protected database and sent with local Internet connection to D-Heart Scientific Team supervised by Prof. Perlini for report.
Each tracing would be carefully analyzed by two independent, blind and impartial observers and stratified according to a score, validated by Del Cre et al. (6) based on the sum of 9 criteria:

1 — Presence of a non-sinusal cardiac rhythm;

2 —Length of QRS ≥110ms;

3 — Presence of LAE, LBBB, defined as QRS>120 ms togheter with R wide R wave and monofasic in DI or V5 and absence Q wave in DI or V5), RBBB, defined as QRS>120 ms together with 'slurred' S wave in DI or V5);

4 —ST/T Segment Anomalies;

5 —ST/T Segment Elevation ≥ 0.2 mV;

6 —Corrected QT interval;
7 — Presence of Pathologic Q waves;
8 — Absence of physiologic Q waves in DI and V5;
9 — Presence of Atrioventricular Block of any degree.

The ECGs would be subdivided in 4 groups:

- Group 1: ECG normal (0 Criteria);
- Group 2: ECG slightly abnormal (1-3 Criteria);
- Group 3: ECG moderately abnormal (4-6 Criteria);
- Group 4: ECG markedly abnormal (7-9 Criteria).

The abnormal tracings would be sent back to Lacor Hospital for referral of the specific patient to further cardiological investigations.

The investigators will receive an appropriate training to use the D-Heart electrocardiograph properly and a course on the interpretation of the ECG.

Educational Perspectives:

Prof. Perlini's team, together with D-Heart Scientific Team would provide a detailed course on ECG interpretation to the Staff of Lacor Hospital willing to collaborate. The course would be held by means of teleconferences from Pavia to Lacor.
The topic expected to be covered during the course are:

- The Normal ECG;
- Impulse Conduction Delays;
- The ECG in myo-pericardial disorders;
- How to recognize the Ischemic patient;
- Arrhythmias identification.

Each lecture is expected to last approximately 1 hour and the target are not only doctors but also paramedical staff willing to participate.

PATIENTS SELECTION: Inclusion Criteria:

- Patients > 17 years old affected by hypertension, diabetes mellitus.

Exclusion Criteria:

- **Patients presenting to the hospital or outpatient clinic in emergency would not be enrolled.**

NUMBER OF PATIENTS TO BE ENROLLED: the present study would require 350 patients.

Current sample calculation has been carried out based on the primary endpoint, hypothesizing an error of approximately 1% with a confidence intervals of 85%. Moreover, practical consideration involving study population size, including considering a total of 20 working days per month, with a total of 60 working days, meaning 5-6 patients per day, which seems pretty reasonable

DATA MANAGEMENT AND ANALYSIS

Each of the study patient would be assigned a specific study ID and their data would be stored in a protected database containing only anonym patient ID. The access to the database would be given only to the list of investigators present in the protocol.

Data analysis support would be provided by D-Heart Team at the end of the study enrollment.

EXPECTED RESULTS: this is the first telemedicine study that enables Lacor Hospital and Pavia to work together simultaneously in the identification of high cardiovascular risk patients. The simple and effective screening method proposed, if correctly validated will provide a reasonable approach to the early detection of renal and heart failure.

STUDY DURATION: The enrollment will take three months, ranging from March, 2017 to May, 2017.

PLANNED ACTIVITIES:

1. Clinical work on the wards
2. Data collection.

Pavia, --/--/--

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