UNIVERSITÀ POLITECNICA DELLE MARCHE

Master of Science in Biomedical Engineering

Extracorporeal Home Hemodialysis: Evaluation of a New Approach to Kidney Disease Treatment

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Abstract

The prevalence of chronic kidney disease (CKD) is estimated to be 8-16% worldwide. With an aging population, and rising levels of hypertension, diabetes and obesity, renal diseases pose an increasing burden on public healthcare. In Italy, the annual direct treatment cost of a patient on dialysis was estimated to be around € 40000 specifically € 29 800 for peritoneal dialysis and €43 800 for hemodialysis. The economic impact of dialysis on the Italian National Health Service (NHS) was estimated to be € 2.1 billion per year. Home dialysis treatments constitute an optimal form of therapy due to the same purifying efficacy with respect to the hospital one, better patients rehabilitation, better integration in the socio-cultural context in which they live and the possibility of maintaining work and social activities. In the context of home dialysis, different technologies and equipment are available in the market. Among them, DIMI offers several advantages for the patient and represents an innovation for home hemodialysis treatment due to its great flexibility in the choice of treatment needed by the patient.

The new DIMI device was used in December 2019 in fourteen prevalent patients with kidney failure aged (68 ± 11) years, attending the dialysis unit of the university hospital of Chieti. Eleven patients underwent a session of hemodialysis with a lactate-based dialysate volume of 20 liters, using a high-flux polyethersulfone hemodialyzer (Dimysis 017, Infomed). Two patients underwent a session of 4 hours and another one on a session of 3 hour. Only one patient underwent a hemodiafiltration session of 2.5 hours.

The aim of this study is to carry out an evaluation of extracorporeal home hemodialysis analyzing blood chemistry tests of population described above. Parameter taken into account and analyzed in this work are: Blood urea nitrogen (BUN; mg/dl), Creatinine (mg/dl), Potassium (mEq/l), Sodium (mEq/l), Calcium (mg/dl), Lactate (mmol/l), pH, Kt/V and Urea Reduction Ratio (URR; %). All of these parameters are considered a marker of dialysis adequacy and were compared with the literature. In the results the same variation of the blood-related parameters as present in the literature has been evidenced. The results found, evidencing the potential benefit associated to the use of the DIMI device, seem encouraging in filling the gap in the market for a machine that can allow different home blood purification treatment.

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1. Introduction

The prevalence of chronic kidney disease (CKD) is estimated to be 8-16% worldwide with an aging population, and rising levels of hypertension, diabetes and obesity, renal diseases pose an increasing burden on public healthcare [1]. Furthermore, kidney disease represents an independent risk factor for cardiovascular mortality. The functional unit of the kidney is the nephron, which is closely integrated with the renal blood supply. The human kidney filters 180 liters of plasma through its glomeruli and produces 1 to 2 liters of urine daily. Approximately 99% of filtered sodium is retrieved as it passes through various sections of the nephron before reaching the collecting duct.

For a small proportion of people with CKD, the kidneys will eventually stop working. The transition from one CKD stage to the next is associated with an increased clinical and economic burden. One of the options when CKD stops the kidney work is dialysis that is a method of removing waste products and excess fluid from the blood. An alternative to dialysis for people with severely reduced kidney function is a kidney transplant. This is often the most effective treatment for advanced kidney disease, but it involves major surgery and taking medicines (immunosuppressants) for the rest of life to stop your body attacking the donor organ.

In general dialysis treatments are performed in hospital, in a specific dialysis department. The most used dialysis technique are hemodialysis and peritoneal dialysis. Hemodialysis, usually done 3 times per week for about 3-4 hours at a time, consist in a circulation of the blood outside the body of the patient making the blood flow through one or more purification element (i.e., dialyzer) and follow up, if necessary, part or all of the removed substances. Instead, peritoneal dialysis is a type of dialysis which uses the peritoneum in a person's abdomen as the membrane through which fluid and dissolved substances are exchanged with the blood. It is done both in hospital and home usually performed daily with 4 to 5 exchanges either manually during the day (CAPD) or nightly with a machine (APD).

Two million people worldwide are currently on renal replacement therapy (RRT), that represent a burden on the NHS i.e number of hospital beds, healthcare personnel and support activities (patient transport to dialysis centers, environmental logistics, material storage). In Italy, the annual direct treatment cost of a patient on dialysis was estimated to be around € 38 821.4 specifically € 29800 for peritoneal dialysis and €43 800 for hemodialysis. The economic impact of dialysis on the Italian National Health Service (NHS) was estimated to be € 2.1 billion per year [2].

In the period of lockdown imposed by the COVID-19 pandemic, the difficulties of countering the spread of the contagion were added to others already in place, due to the tendency of the National Healthcare system to focus mainly on hospital activities to the detriment of territorial medicine.

The National Plan of Chronicity, approved by the Italian State-Regions Conference, refers to the topic of home care, specifying how the fundamental objective of chronic care systems is to keep the sick person at home as long as possible [1]. Home dialysis treatments constitute an optimal form of therapy characterized by the same purifying efficacy with respect to the hospital one, better patient rehabilitation, better integration in the socio-cultural context in which they live, and the possibility of maintaining work and social activities [2]. Currently, home dialysis, both peritoneal one and hemodialysis, involves safe high quality technological systems, supported in the most advanced centers by telemedicine, and allow people with CKD to perform replacement therapy safely at home. In the other hand not all systems actually on the market are able to perform all kind of therapy needed by the patient such as hemodiafiltration, ultrafiltration and hemofiltration.

Infomed, a Swiss company based in Geneva dedicated to the development and manufacturing of blood purification devices since 1997, presented on the market a new device for home hemodialysis called DIMI. It offers several advantages for the patient and represent an innovation for home hemodialysis treatment due to its great flexibility in choice of treatment needed by the patient.

In the Chapter 2 of this thesis was analyzed renal pathophysiology and its "epidemic" increase in world's population. After has been analyzed the different renal replacement therapy to counter CKD, home hemodialysis approach has been studied in the Chapter 3 as an alternative approach to the standard therapies. The Chapter 4 of this thesis deals with the presentation of the DIMI system, utilized 14 patients in the dialysis unit of the University Hospital of Chieti, that represent a new generation of home dialysis machine capable to perform also therapies considered hospital prevalently. The aim of this thesis was to carry out an evaluation of the home hemodialysis analyzing blood chemistry tests of 14 prevalent patients effected by kidney failure, aged 68 ± 11 years, in the dialysis unit of the University Hospital of Chieti. Parameter taken into account and analyzed in this work are: Blood urea nitrogen (BUN; mg/dl), Creatinine (mg/dl), Potassium (mEq/l), Sodium (mEq/l), Calcium (mg/dl), Lactate (mmol/l), pH, Kt/V and Urea Reduction Ratio (URR; %). The system used was the DIMI developed by Infomed. It was decided by virtue of several interesting reasons discussed in this work.

2. Renal pathophysiology

Chronic kidney disease (CKD) is defined as "a condition of altered renal function that persists for more than 3 months", classified in five stages of increasing severity, is a pathological condition associated with a high risk of mortality and morbidity.

It is defined as a reduction in glomerular filtration rate, increased urinary secretion of albumin, or both, and represents a growing public health problem.

It is estimated that 8-16% of the world's population is affected by CKD [3].

The reasons for this increase, which is defined as "epidemic" from some health systems, are manifold [2]:

- the ageing of the population contributes to increasing the rate of patients, as a physiological consequence related to the aging of the kidney;
- the increase in the general population of diseases leading to a kidney damage (type II diabetes mellitus, metabolic syndrome, high blood pressure, obesity, dyslipidemia) and increased survival of patients themselves;
- CKD diagnosis facilitated by the availability of simple, reliable, and low-cost diagnostic tools.

It has been found that only a part of patients with CKD is intended for substitution treatment (hemodialysis, peritoneal dialysis and transplantation) because most of them have heart attacks or strokes before they can start replacement treatments [3]. Furthermore, although renal transplantation is the best way to restore the renal function, only a minority of patients who start dialysis treatment can be a candidate, due to the co-morbidities that they present. The interest in dialysis, therefore, is justified not only by the clinical and social impact of the treatment itself, but also by the costs, which account for 3-5% of all public health expenditure [4].

2. 1 Kidney

The kidneys are two symmetrical organs located in the abdominal cavity at the sides of the last thoracic vertebrae and the first lumbar vertebrae, about 10 cm long, 7 cm broad, 3 or 4 cm thick, and weighing about 150 grams each one (Figure 1). Kidney receives large amounts of blood from the renal artery and, after filtering it, pours it into the renal vein that flows into the vena cava. The functional unit of the kidney is the nephron able to filter the blood and collect the filtrate that will give origin to urine. The final product of filtration flows into the renal pelvis and then, through the ureter, into the bladder, where it accumulates before being excreted through. Four fundamental processes take place in the nephron and they are:

- FILTRATION: occurs between glomerular capillaries and Bowman's capsule. To perform this function, during the day the kidneys filter a huge amount of plasma (about 180 liters), and then operate a selective resorption of substances that should not be eliminated.
- RESORPTION: consists in the recovery of water and filtered solutes, which pass from the tubules to the blood capillaries.
- SECRETION: process, inverse to resorption, whereby some substances pass from the blood contained in the capillaries to the renal tubules.
- EXCRETION: consists in the elimination of urine in the renal pelvis. The excreted volume is the filtered volume minus the reabsorbed volume plus the secreted volume.

The main renal function, besides the removal of waste products, is above all the homeostatic regulation of the water content and ions in the blood, also called hydroelectric balance. The kidneys, in fact, maintain the normal concentrations of water and ions balancing the supply of these substances with their excretion in the urine, according to the principle of mass conservation.

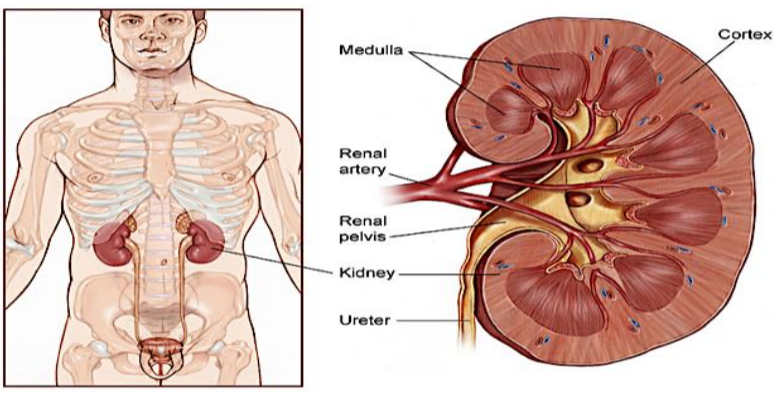

***Figure 1**. Kidney*

2.2 Kidney failure

Chronic kidney disease (CKD) is divided into 5 stages based on the level of residual kidney function (Table 1). Stages are determined through certain tests including a test used to calculate glomerular filtration rate (GFR), which measures how well your kidneys are cleaning your blood. Kidney disease is a progressive disease, meaning that kidney function can continue to decline over time, eventually resulting in kidney failure.
Kidney failure is a condition in which the kidneys fail to ensure the normal disposal of waste and normal composition of body fluids. Severe kidney diseases can be divided into two main categories:

- Acute kidney injury (AKI): the kidneys abruptly stop their functionality in a complete or almost complete way but may resume normal function.
- Chronic kidney disease (CKD): progressive loss of function of an increasing number of nephrons, which gradually decreases the general renal function.

Within the two main categories, there are many specific kidney diseases that can affect kidney blood vessels, glomeruli, tubules, the renal interstice and part of the urinary tract outside the kidneys, including ureters and bladder.

Table 1: *The five stage of kidney disease*

Five stages of kidney disease		
	Kidney function/GFR	
Stage 1	>90%	Normal or High Function
Stage 2	60-89%	Mildly decreased function
Stage 3	30-59%	Mild to moderately decreased function
Stage 4	15-29%	Severely decreased function
Stage 5	<15%	Kidney failure

2.3 Renal replacement therapy

When the kidneys are no longer able to perform their function, and waste substances and fluids that the kidney cannot eliminate, it is necessary to replace the renal function by removing the toxic substances (waste) and the excess liquids. This is obtained through different renal replacement therapies, that are necessary when more than 90% of the normal renal function is lost. During the early stages of chronic renal insufficiency, efforts are made to preserve the function of the organ as long as possible, to delay the need to start a replacement therapy. Replacement therapies in based on the external blood purification method.

Extracorporeal blood purification consists in removing selected substances from the blood through three separate steps:

- Circulation of the blood outside the body of the patient
- Making the blood flow through one or more purification element (i.e. dialyzer)
- Follow up, if necessary, part or all of the removed substances

Typically, the removed substances are:

- Small molecules accumulated during heart failure and/or kidney failure:
    - Water
    - Salts (sodium, potassium, chloride)
- Medium molecules derived from sepsis, surgical operation, intoxication:
    - Uremic toxins
    - β_2- microglobulin
- Large molecules:
    - Low-density lipoprotein (LDL)
    - Fibrinogen
    - Immunoglobulin (IgG, IgM)

Renal replacement therapy includes dialysis (hemodialysis, peritoneal dialysis), hemofiltration, hemodiafiltration and ultrafiltration which are various way of filtration of blood. Each of them characterized by specific transport mechanism.

2.3.1 Transport mechanism

The transport of substances through the membrane depends on:

- the difference in concentration of substances on either side of the semipermeable membrane (between the blood compartment and the dialysis compartment or vice versa)
- the hydrostatic pressure of the liquid to be filtered
- the osmotic pressure exerted by the substances present in solution
- the interaction between the semi-permeable membrane and the liquid to be filtered.

The physical-chemical principles that underlie this transport from one side to the other of the semipermeable membrane are: diffusion, filtration and convection, osmosis and adsorption.

Diffusion

Diffusion is the migration of molecules, caused by random movement, from a region of higher concentration to a region at lower concentration. This means that the diffusion flux J (molecules/m^2s) per area unit (A) is proportional to the concentration gradient C (molecules/m^3), which is the "driving force" (driving force):

$$\frac{J}{A} = -D \times \frac{\Delta C}{\Delta X} \tag{1}$$

where D (m^2/s) is a single solute diffusion coefficient, negative sign expresses the movement from higher concentration to lower one and ΔX is the distance between the two regions (thickness of the membrane that the solute must pass).

Filtration and convection

Ultrafiltration refers to the passage or transport of the solvent (plasma water) from one side of the membrane to the other one. To obtain ultrafiltration, a difference in hydrostatic pressure is required, which is applied by means of pumps in the dialysis machine. The ultrafiltration flow Q_{UF} (l/h) is expressed according to the characteristics of the membrane and the pressure gradient:

$$Q_{UF} = K_{UF} \times \Delta P \tag{2}$$

where K_{UF} is the coefficient of permeability of the membrane and ΔP is the transmembrane pressure (TMP).

TMP (mmHg) is defined by:

$$TMP = \frac{(P_{B\_IN} + P_{B\_OUT})}{2} - \frac{(P_{D\_IN} + P_{D\_OUT})}{2} - P_{ONC} \tag{3}$$

where P_D and P_B are, respectively, the mean hydrostatic pressures in the dialysate and blood compartment and P_{ONC} the oncotic pressure in the blood compartment.

Osmosis

Osmosis consists of the transport of the solvent through a semi-permeable membrane from the side in contact with the diluted solution to the side in contact with the concentrated solution, and the driving force is the chemical potential difference between the solutions on each side of the membrane.

Adsorption

The adsorption phenomenon refers to a direct interaction between the biological fluid and the dialysis membrane. The adhesion of solutes, in particular proteins, on the membrane surface of the filter can be considered as both a positive and a negative aspect. On the one hand, in fact, there is the possibility, through chemical-physical interaction, of eliminating, substances and solutes that are harmful to the dialyzed patient (such as β-2-microglobulin), on the other hand, the resulting steric size can reduce the flow of diffusion and convection.

2.3.2 Dialysis

Dialysis consists of a physical process capable to separate molecules in solution through the use of a semipermeable membrane. The aim is to remove excess toxic substances or at least to keep their plasma concentration below levels considered toxic. This method is called "extracorporeal" dialysis. The blood taken from the patient through a vascular access, flows in an externally circuit, then it is purified through a filter (containing the membrane) and finally reinfused back.

2.3.2.2 Hemodialysis (HD)

The main removal of solutes in hemodialysis is based on the diffusion mechanism, particularly suitable in the small solutes discard. Hemodialysis involves the use of a filter where blood and an appropriate dialysis solution circulate counter-current or, less frequently, co-current. The counter-current configuration is generally preferred because the mean concentration gradient is maintained high throughout the length of the dialyzer. Conversely, the co-current configuration ensures better stability and control of hydrodynamic conditions, as well as more effective priming [4].

High flow dialysis can produce significant convective transport: this mode is called high flow hemodialysis (HFD). Patients undergoing hemodialysis usually perform the treatment in hospital for 3 times a week, and each session lasts about 4 hours, with shifts in the morning or afternoon. Such type of treatment can be performed in hospital, Limited Assistance Center (CAL) and at home.

2.3.2.3 Peritoneal dialysis

Peritoneal dialysis (PD) is an alternative therapy to the extracorporeal one, which uses the peritoneum in a person’s abdomen as the membrane through which fluid and dissolved substances are exchanged with the blood. There are two main methods to apply this kind of dialysis: continuous ambulatory peritoneal dialysis (CAPD), which involves manual exchanges, and automated peritoneal dialysis (APD), where exchanges are managed automatically by the machine. In order to perform peritoneal dialysis, it is necessary to insert surgically, under local anesthesia, a small silicone catheter in the abdominal cavity in order to allow the entrance and the exit of the dialyzing fluid. The CAPD is a continuous method and the treatment consists in filling the abdomen with a dialysis fluid, contained in special bags, and emptying it after a stop of about 6 hours. Typically, 4 evenly distributed exchanges in a day are needed. The APD method involves the connection of the peritoneal catheter to a membrane (cycler) which automatically exchanges the fluid in the abdomen. The PD patients in general perform the therapy at home, CAPD 3-5 exchange a day and APD overnight. In PD, the caregiver is only needed for catheter dressing (3 times / week 30mn), but only 40% of patient are candidate for this therapy [5]. Nowadays PD is the first choice for home dialysis treatment, but home hemodialysis represents an alternative for those patients who cannot benefit of PD.

2.3.3 Further renal replacement therapy

AKI in critically ill patients is rarely monosymptomatic: in fact, it is a consequence of a multiorgan dysfunctions. Treatments in these cases cannot be based on "standard" dialysis. In fact, ad hoc methods are developed to have good tolerability from a clinical point of view, good purifying capacity of various uremic toxins and maximum ability to correct hydro-electrolytic and acid-base homeostasis. These renal replacement therapies, used principally in the intensive care unit, are:

- Hemofiltration
- Hemodiafiltration
- Ultrafiltration

2.3.3.1 Hemofiltration (HF)

Hemofiltration is an exclusive ultrafiltration/convection treatment, where no dialysis fluid is used. The infusion of a sterile solution into the blood circuit replaces the plasma volume eliminated and reduces the concentration of plasma solutes. The infusion of sterile solution (replacement fluid or reinfusion solution) can totally or partially replace the filtered volume. The replacement fluid may be infused prefilter (pre-dilution) or post-filter (post-dilution). Permeable membranes are used. The volume removal obtainable over time by ultrafiltration depends on the K_{UF} of the membrane. In terms of removal of solutes, the post-discharge mode is more efficient than the pre-dilution mode; however, it can more easily be associated with membrane choke due to increased hemoconcentration. The clinical benefits are improved cardiovascular stability and better efficiency of β_2-microglobulin removal with reduction of uremic amyloidosis. Its limitation is the low removal of small molecules, which depends on the ultrafiltrate volume, so a large volume of reinfusion solution is needed to obtain an appropriate Kt/V leading to high cost and an increased time

2.3.3.2 Hemodiafiltration (HDF)

Cardiovascular instability continues to represent the most frequent acute complication during dialysis treatment, while pathology due to accumulation of β_2-microglobulin and accelerated atherosclerosis are the most important long-term complications impacting heavily on morbidity and mortality which varies between 14 and 26% in Europe [10]. Hemodiafiltration combines HD and HF, so the mechanisms involved in the removal of solutes are both diffusive and convective which allow to combine the advantages of the removal of low molecular weight solutes (by diffusive way) with the advantages related to the removal of medium / high molecular weight substances (by convective way). This mode uses highly permeable membranes; an adequate amount of sterile replacement solution should be infused to replace the removed volume, both in pre- and post-filter. The HDF treatment has clinical advantages related to the biocompatibility characteristics of the type of membrane used and the advantages demonstrated by numerous clinical studies related to convective treatments such as: greater cardiovascular tolerance, a reduction of intradialytic complications, a more efficient control of anemia with reduced consumption of erythropoietin, fewer problems related to amyloidosis formation, higher values of Kt/V. Therefore, HDF is increasingly used in several AKI settings such as septic AKI, rhabdomyolysis-associated AKI, myeloma cast nephropathy, and contrast-induced AKI. Hemodiafiltration, thanks to the multiple benefits on cardiovascular risk factors in dialysis patients, is nowadays, the most effective dialysis method and which is closest to the elimination profile of the natural kidney. However, for many years the method was poorly used due to both technical and economic limiting factors. In fact, this technique is supposed to have an additional cost which may be an obstacle to increase its development in dialysis centers, in fact single cost treatment it was estimated to be 348 €.

2.3.3.3 Ultrafiltration (UF)

Similar to dialysis, ultrafiltration is a type of renal replacement therapy that may be indicated for patients with heart failure who have significant volume overload despite outpatient diuretic therapy. The main objective of the UF is the removal of liquids, using a pressure gradient through a highly permeable membrane, without replacing its volume. Ultrafiltration removes solutes in terms of mass, but not concentration. Patients must meet specific criteria to be considered as candidates for ultrafiltration. Adults with heart failure and signs and symptoms of significant volume overload despite outpatient diuretic therapy and prior hospitalization for heart failure may be considered for ultrafiltration. Hemodynamically unstable patients and those experiencing an acute coronary event, such as myocardial infarction, should be excluded from ultrafiltration.

2.3.4 Transplantation

Surgery and renal transplantation (from donor or corpse) are the last of the possible CKD treatments. It is obviously an invasive operation and brings with it all the problems related to an anti-rejection therapy, which in any case will not be treated here.

2.4 Therapy

From a practical point of view, it is useful to distinguish two dialysis circuit: the blood circuit and the dialysate circuit.

The blood circuit consists in the following components:

- vascular access
- blood line (venous and arterial)
- arterial pressure detector
- venous pressure detector
- pumps
- heparin pumps
- filter
- air detector

Vascular access

Good vascular access to the patient is essential for performing dialysis. It is important to obtain sufficient blood flow to avoid clotting and complications and this is achieved through anastomosis between an artery and a vein (shunt).

Current literature suggests the arteriovenous fistula to be the preferred type of vascular access for hemodialysis. Once established, fistulas have longer patency and lower rates of complications compared with arteriovenous grafts and catheters [6].

The current focus on patient-centered care requires individualized approaches to therapy, including the choice and use of vascular access, on the basis of each patient's unique balance of risks and benefits. As such, complications related to vascular access also deserve careful consideration.

Fistula complications are associated with morbidity, mortality, and a high economic burden [6].

Blood line

During the treatment, the blood flows within lines that allow the passage of the same to the filter and then, once purified, the patient.

The single-use blood lines are divided into arterial and venous, with the joints characterized respectively by red and blue color: the arterial blood line connects the point where the arterial needle-cannula penetrates (blood extraction) with the filter, while the venous blood line connects the filter with the point where the venous cannula needle penetrates (blood return).

The blood lines, both venous and arterial, consist of biocompatible and non-toxic material, usually polyvinyl chloride (PVC). Along both lines there are clamps that are used to block the circuit in case of alarms by the machine.

Pressure detectors

The pressure inside the circuit is a fundamental parameter during the monitoring of an extracorporeal dialytic treatment. In the specific case, the arterial component tracks the pressure between the arterial vascular access and the blood pump, while the venous one between the dialysis filter and the venous vascular access.

Blood pressure should not be too low (maximum limit up to -150 mmHg) either to avoid the collapse of the shunt vessel wall on the arterial needle or to minimize the risk of air aspiration in blood lines.
Instead, the arterial pressure is a positive pressure that depends on the speed of the blood pump and the resistance of the shunt and needle venous cannula.

Pumps

One of the most critical components of dialysis systems is the pump for the extracorporeal circulation of human blood which is subject to several constraints such as sterility requirements, biocompatibility, flow rates, reliability, energy efficiency and low cost.
Peristaltic pumps, commonly used in traditional hemodialysis machines, play an important role among the pumps, in which moving rollers squeeze a flexible tube forcing the fluid in one direction. Peristaltic pumps (roller) have the following advantages: a high level of sterility because blood is in contact only with the flexible tube, it is not necessary to introduce a flow meter into the circuit since by imposing the number of revolutions of the pump it is possible to estimate directly the flow rate. The main disadvantages of rollers traditionally used for hospital dialysis are their size, weight and very poor efficiency due to the large energy losses coming from squeezing process.
Another interesting type is represented by diaphragm pumps in which the positive displacement is due to the oscillation of a membrane in a compression chamber with valves. This type of pump shows high efficiency and compactness. In particular, the study of Longo shows how peristaltic pumps feature an electrical energy consumption 2-4 times higher than that of diaphragm pumps [7].
This dramatic difference is due to the principle of operation of peristaltic pumps, the squeezing process, which is intrinsically influenced by large energy dissipation effects. The overall efficiency of a peristaltic pump is remarkably low and ranges from a maximum value of 9-10%, at higher flow rates, to a minimum constant value around 0.3% at very low flow rates. In fact, at very low rotation speed, all the power supplied to a peristaltic pump is dissipated by friction in the squeezing process. The overall efficiency of diaphragm pumps increases with capacities between 1% and 20% and is 2-4 times higher than that of peristaltic pumps.

Heparin pump

In a dialysis circuit, blood comes into contact of different artificial devices. Due to this, clotting or coagulation phenomena can occur, with dangerous consequences for the health of the patient. To avoid them, medications are used.

Heparin is an anticoagulant drug that can, as such, slow or stop the blood clotting process. During dialysis treatment, the dose of heparin to be administered varies from patient to patient.

Dialyzer filter

The filter is the "heart" of the dialysis and extracorporeal circuit called "artificial kidney". In it, exchanges and transport phenomena occur, that allow the blood to be purified.

Prerequisite for any biomedical product is biocompatibility; in the specific case of filters, they must respond to specific properties to ensure blood compatibility. The filters currently available are mostly hollow fibers and mainly identified by geometric and performance characteristic. The ultrafiltration coefficient of the filter depends largely on the material used for the membrane and the size of the pores. High-flux filters are those in which the ultrafiltration factor is higher than 20 ml/h/mmHg, lower-flux filters have this factor lower than 20 ml/h/mmHg. Synthetic polysulfone and polyethersulfone membranes are the most versatile and have had the greatest success on the market.

The choice of the filter depends on many factors, one of the most important is the patient's biocompatibility and patient clinical needs reducing the risk of anaphylactic reaction. In fact, episodes of intolerance to a specific filter can often occur, it is therefore important to have a machine capable of using a wide range of filters.

Air detector

The presence of air bubbles inside the circuit can cause emboli formation and must be absolutely avoided. For this reason, wells are used along the blood lines, both arterial and venous ones, so that the air, less dense than the blood, can be eliminated. A well makes use of an ultrasonic technology: if the spread of ultrasounds, which easily pass through the blood, decreases below a predetermined threshold due to the presence of micro air bubbles, it triggers the alarm in the machine and, simultaneously, by closing an automatic.

Time treatment

Patients that undergo HD have to access the hospital center 3 times weekly for a 4-hour single treatment, while patient in PD in general perform the therapy at home, CAPD 3-5 exchange a day and APD overnight. In general, it will be necessary for patients organize times to continue to carry out their work since they must go in hospital. Travel can be limited and going on vacation can be a problem.

HF is usually indicated in case of fluid overload, congestive heart failure, acute renal failure, crush syndrome, lactic acidosis. But HF may also be successfully used for patients with chronic renal failure. This therapy is usually performed according to the same protocol as hemodialysis, at least 3 times per week and up to 7 times for 2-8 hours.

Continuous slow ultrafiltration is used when the only requirement is water removal. In fact, it is a continuous dialysis with a low filtration rate. It can remove up to 6 liters of liquid per day. Usually, UF is usually performed from 4 to 8 hours, until the targeted water volume to remove from the patient is reached.

The HDF is performed in hospital, usually in intensive care units, with the infusion of sterile and non-pyrogenic liquids through a system that allows the supply at the moment (online) of the necessary infusion volume, prepared from the dialysis liquid. This technique nowadays is performed only in hospital, usually three times a week, for a time treatment similar to standard hemodialysis at least 3 times per week and up to 7 times for 2-8 hours. It is evident that approaches in which the patient can carry out the therapy without several moving and in which the patient has greater flexibility in choosing the time of day to perform dialysis, guarantee more freedom in dailylife. For this reason, patients often feel better, both emotionally and physically, after switching from in center to home dialysis [8]. Frequent hemodialysis improves survival and quality of life and home hemodialysis facilitates frequent therapy [9]. Therefore, adding convective therapies to home hemodialysis could improve treatment quality [10].

3. Home hemodialysis (HHD)

A factor that will characterize the healthcare world in the near future will be the increase in chronic diseases: if not properly addressed, this factor will also result in an increase in access to healthcare facilities and a request for greater medical and assistance capacity. Healthcare therefore faces an inevitable increase in costs due to both the number of services to be provided and the growing demand for quality of services. In the particular case of dialysis, it should be considered that it is a "life-saving" treatment. At a strategic level, the quality of life of the patient is strongly influenced by his ability to live with this serious disease for a long time, even in terms of costs. In fact, it was estimated in 2016 that in Italy the total annual social cost of the CKD was € 1,809,552,398 that represents the 0.11% of gross domestic product [11].

Tucchetti et al. in their study analyze the cost of assisting patients with a CKD in stage 4 and 5 in the only region of Tuscany [11]. Overall, the estimated average annual social costs of a single patient with CKD were € 9514.8 for stage 4, and € 11,152.4 for stage 5. Non-medical direct costs and indirect costs represent, respectively, 32% and 26% of the total social cost for CKD in stage 4, and 26% and 27% in stage 5. Direct costs amount to € 1,692,267,579 (due to the medical component of € 1,001,955,049 and the non-medical component of € 690,312,531) and indirect costs of € 117,284,819. The results of the study show that economic assessments which quantify only direct medical costs give a limited view of the phenomenon. The assessments of the economic burden of CKD have to be based on all cost items in order to estimate the real amount of social costs.

In particular, the costs on the National Health System (NHS) of patients with chronic renal insufficiency is evaluated by direct costs (health and non-health) and indirect costs:

- direct (personnel costs, materials, maintenance, non-service equipment, medicines and medical examinations)
- indirect (transport services, hotel services, general services)
- social

In this complex scenario, home dialysis represents an innovative approach to dialysis therapy that can overcome all of these problems. Extracorporeal Home Hemodialysis (HHD) is not yet well known in the panorama of substitution treatments for chronic renal insufficiency. This type of dialysis modality, already used in other Countries and in some Italian Regions, can offer significant advantages in terms of clinical results, socio-economic and quality of life of the patient.

From the literature, we can see important clinical-social reasons to activate/expand programs of extra-corporeal hemodialysis at home:

- Improved quality of life and social rehabilitation: personalized treatment allows full-time reintegration into work [12].
- improvement of depressive symptoms and shorter recovery time from asthenia in the post-dialysis period [13].
- improvement of sleep disorders and restless leg syndrome [14].
- lower stress on heart activity and reduction of left ventricular hypertrophy [14].
- better control of high blood pressure and reduced use of anti-hypertensive drugs [15].
- reduction of morbidity and mortality [16].

From the economic and social point of view, the costs of hospital hemodialytic treatment do not concern only technical equipment (direct costs), but also the employment of medical-nursing staff, vocational training (human costs) infrastructure, transport, concomitant treatment (indirect costs). In addition, there are costs associated to the travel of the patient to the treatment center, several times a week, with a loss of working days and finally a malaise and anxiety that affect interpersonal relationships (social costs). The success of home dialysis therapy, which, as observed, reduces the costs borne by the NHS, is closely linked to the selection of the patients and their caregivers, following the NICE (National Institute for Health and Care Excellence) guidelines. The patient must be strongly motivated to learn the necessary procedures and to accept the modalities of home treatment, but his/her clinical conditions must not make the domestic environment not suitable and dangerous for the conduct of therapy. Additionally, the patient equipped with a vascular access for extracorporeal hemodialytic therapy, must show good intra-dialytic cardiovascular stability. Regarding home, the electrical system must be up to standard and properly grounded. The caregiver (family member, friend, volunteer) must be predisposed and suitable to carry out a training phase and to help the patient in the management of hemodialytic treatment.

3.1 Home dialysis machine

When home hemodialysis (HHD) was first developed in the 1960s, the equipment was large and difficult to use. But new technological advances have made machines and water treatment equipment available for home hemodialysis (HHD) patients more reliable and user-friendly. This new generation of machines is easier to set up, clean and disinfect while offering increased flexibility and a much more comfortable experience for patients. The newest home hemodialysis machines are designed to take up less space and require fewer supplies, meaning less required storage space. Some new equipment options are also designed to provide more portability, allowing patients the ability to travel for work or leisure with their machines.

A home hemodialysis machine removes waste and fluids from the body when the kidneys no longer work well enough to keep the body healthy.

Hospital hemodialysis (HD) treatment is usually performed for 4 hours thrice a week. Increasing dialysis frequency and duration has a number of positive effects. Helen J Jefferies et al. in their show better blood pressure control, cognitive and sexual function and reduced anemia, myocardial stunning, left ventricular hypertrophy and sleep apnea [17]. As a matter of fact, home HD offers the ability to increase the hours and frequency of treatment. Recent data, including those from randomized controlled trials, suggest that the benefits of more frequent dialysis are similar to kidney transplantation, including greater solute clearance, better volume control potentially reducing left ventricular hypertrophy, improved nutrition, and improved quality of life [17].

The most important hemodialysis machines currently in the market are: Infomed's Dimi blood purification device; NxStage, used for more than 10 years on the American market and in France since 2012, and S3 by Physidia, used since 2013 in France with a European development program begun in 2017.

3.1.2 Monitoring

One of the disadvantages of any home dialysis treatment is the potential risk that patients, without a frequent monitoring readily available during centralized dialysis, may receive inadequate treatment. Low adherence to therapeutic prescriptions was observed by

Bernardini et al. who reported that 30% of their peritoneal dialysis patients did not meet the prescriptions. Ideally, if the home treatments of PD patients could be monitored on a daily basis, this would make it possible to detect problems and correct the administration of inadequate dialysis [18]. Technology solutions for remote monitoring of home dialysis treatments are now available; such programs allow physicians to learn about many aspects of the therapy at the patient's home in real time. Based on information obtained through remote monitoring, the clinical team can provide advice and propose interventions that allow patients to obtain safer and better-quality treatment.

These remote patient monitoring (RPM) systems could give more confidence and satisfaction about the care treatment, from the point of view of the patient who knows he is being monitored and adequately supported. Thus, RPM has the potential to improve therapy outcomes and confer economic benefits. One of the new technologies that has enabled a leap forward of RPMs is a connectivity platform which is a global family of cloud-based products for medical devices.

The platform securely communicates with the home dialysis machine and allows authorized users to remotely view and manage processing information sent by a machine. Authorized users can also remotely program the therapy that will be performed.

To improve the confidence of the doctor, the organization and presentation of treatment data are provided for a real time evaluation, allowing the doctor to review the results of treatment, evaluate the therapy and assess the status and compliance of the patient.

This kind of technology can be also able to provide the doctor with the ability to remotely adjust the settings of the device as needed to maintain the appropriate therapy for their patients. Travel is an important obstacle for many patients when it comes to receiving good health care. Frequent home visits are a way of reducing the workload. Frequent patient-supplier interaction has been shown to lead to a reduction in both hospitalization for specific reasons and recurrent ones.

However, increasing patient-provider interactions through home visits can be expensive. RPM can reduce the frequency of in-person interactions since clinical information can be monitored remotely between visits.

Overall, a combination of telemedicine, via videoconferencing, as well as the use of RPMs can help reducing the time and cost burden associated with both in patient travel and the need for home visits.

3.2 Prescription

As it was said before, hospital dialysis is performed 3 times weekly. Contrary, the home dialysis allows to perform the treatment more than three times a week, generally five or six times a week for two to three hours per session. This is due also to the fact that the home hemodialysis machine works at a different flow rate with respect to the hospital ones.

Blood flow

Blood flow (Q_b) is the volume of blood circulating in the extracorporeal circuit per unit time, expressed in ml/min. During treatment, the adjustable blood flow depends on the mode used, the type and quality of vascular access.

Dialysate flow

Dialysis flow (Q_d) is the amount of dialysis fluid flowing through the circuit per unit of time minutes or hours. Q_d is measured in ml/min.

Nowadays there are different kind of HHD machine that work at different dialysate flux (Table 2.).

Table 2. *System low flux vs high flux of dialysate*

	System low flux of dialysate	**System high flux of dialysate**
Q_d max	200 ml/min	800 ml/min
Q_b max	400 ml/min	600 ml/min
Designation	System designed for the home with bags of dialysate ready to use	System designed for hospital with water treatment system
Consumption	20 l	120 l
Assistance	Caregiver	Non-autonomous patients need nursing assistance
Treatment time	2 h, 5/6 times a week	3 h, 4 times a week

The major advantage of the low dialysate volume approach, as intuitive to understand, is the utilization of lower volumes of dialysate to achieve similar clearances. While the weekly dialysate volume used in traditional hemodialysis is around 270 to 600 l per week, at flow rates of 600-800 ml per minute, the low dialysate volume approach utilizes 90 to 200 l per week, at flow rates of 100-200 ml per minute. Possibility of operation with bags, rather than online, avoiding issues such as water quality, installation of the hydraulic circuit and maintenance of dialysis equipment. Several studies report also that a reduced Q_d means no differences in dialysis efficiency [11].

For urea, the saturation of the dialysate with a flow rate <200 ml/min is greater than 90%, and that of phosphorus is greater than 85%. This contrasts with the saturation of the dialysate at a flow rate of 500 ml/min, which is 55% for urea and only 35% for phosphorus. The amount of phosphorus purified per week by conventional hemodialysis is about 3.2 g, while it is 8.1 g for night hemodialysis, assuming 6 nights, and 4.6 g for frequent-dialysate hemodialysis. Thus, the elimination of phosphorus in frequent dialysis is improved thanks to better saturation of the dialysate with a low dialysate flow, more treatments per week and an increase in the total dialysis time (an increase of 15 min dialysis time per day increases phosphorus removal by 8%) [19].

A disclaimer about the utilization of Kt/V to determine dialysis adequacy must be part of all discussions regarding dialysis prescriptions. However, though imperfect, it remains to-date the most widely used measure. One must remember to assess the patient on multiple parameters including symptoms of uremia, volume status, electrolytes, nutritional status, and not just rely on Kt/V to make changes to any dialysis prescription. In the study of Rivara comparing 2 groups of patients, one in conventional dialysis centers and the other one in home dialysis for 5 times/week, 51% of at-home patients had a Kt/V std < 2.1, versus 27% in centers. Despite this, cardiovascular complications, deaths, and hospitalizations were significantly lower in the at home dialysis group. This confirms the Kt/V limit as the sole criterion of adequacy [25]. Prescriptions for more frequent hemodialysis (HD) differ from those for conventional thrice-weekly therapy, partly because of the additional options available to fit individual patient lifestyles. The low dialysate volume approach is based on the principle of the dialysate fluid being nearly completely saturated with urea: by lowering the dialysate flow in comparison to the blood flow, the slower dialysate flows as it opposes blood, the more time is needed for mass transfer and saturation with urea:

$$\text{Fractional Urea Clearance} = \mathrm{K} \cdot \mathrm{t}/\mathrm{V}_{\mathrm{urea}} \quad (4)$$

where the clearance of urea K (ml/min) multiplied by time t (min) yields the volume cleared of urea during a dialysis treatment. This is normalized to the volume of distribution of urea V (ml), the result is a dimensionless parameter called Fractional Urea Clearance.
The saturation of dialysate fluid with urea is determined by the dialysate flow relative to the blood flow. This brings to an important component of the prescription in the low dialysate volume approach, i.e. the flow fraction (FF):

$$\mathrm{FF} = \frac{\mathrm{Q_d}}{\mathrm{Q_b}} \quad (5)$$

The higher the flow fraction, the lower the dialysate urea saturation. With standardization of the flow fraction comes standardization of dialysate saturation for each treatment: this ratio is fixed, which allows for the dialysate flow rate to be adjusted automatically by the machine in response to any changes in blood flow that may occur, without the need for patient intervention, to maintain a desired saturation of urea. The target single pool Kt/V for 3 times a week in-center hemodialysis is about 1.2 to 1.4. Three weekly treatments with a single pool Kt/V would provide a weekly standard Kt/V of about 2.0. It is important to remember that the relationship between single pool and standard Kt/V is not linear and the weekly clearance is not merely the sum of the clearance of each treatment. In home hemodialysis, as the number of sessions per week are higher, the target per session Kt/V is lower, around 0.5 to 0.6, depending on the number of sessions per week, to achieve a weekly standard Kt/V of 2 to 2.2.

Relationship between clearance and fluxes

Home hemodialysis machine is characterized by the presence of significantly lower flows than standard ones. It is important to notice that decreased $\mathrm{Q_b}$ and $\mathrm{Q_d}$ do not means decreased the clearance. In the Figure 2 it is evident that with a Q_d of 200 ml/min, typical value in low-flow dialysis, when Q_d exceeds 200 ml/min the clearance rate K remains substantially stable. Below Q_b equal to 200 ml/min it is recorded the same K rate for 200 ml/min and 800 ml/min of Q_d. So, the increase in Q_b and/or Q_d over 200 ml / min does not cause a proportional increase in K but produces a wastage of liquids.

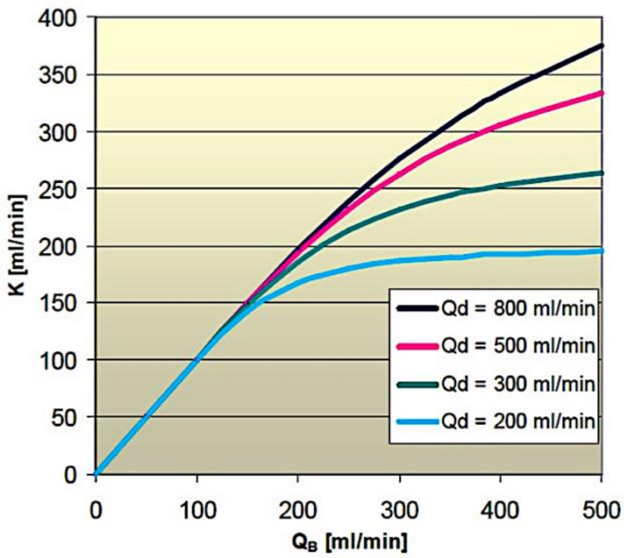

Figure 2. *Clearance is proportional to Q_b until the value 150 ml/min is reached.*

Any hemodialysis prescription requires the following parameters:

- Blood flow
- Dialysate flow
- Dialysate volume
- Body water volume (normally 60% of body weight)
- Volume of waste substance at week
- Concentration of solutes in waste substances relative to the concentration in the blood
- Duration session and number of treatments at week

Filtration Fraction (FF) can also be added as a parameter for home hemodialysis prescription.

4. DIMI

The prevalence of CKD continues to grow internationally, leading to rise in need for renal replacement therapy. HHD offers the opportunity to individualize ad-hoc treatment for patient and to avoid patient moving to the treatment center. However, despite the several benefits highlighted before only a minority of patients in stages 4 and 5 are currently treated with HHD. Reasons primarily include the utilize of HD conventional machine modified for HHD, in fact their complexity has been one of the hurdles reducing the number of patients choosing HHD. Over the last years, however, an alternative generation machine specifically designed for HHD has been developed, with the principal aim of making the interface, setup, and operation more user friendly, without compromising the therapy efficacy and security [20].
Among the new generation machines, DIMI is a portable dialysis machine developed by Infomed for a wide range of therapies including:

- Hemodialysis
- Hemofiltration
- Hemodiafiltration
- Ultrafiltration
- Peritoneal dialysis

DIMI offers the possibility to perform these treatments at home. It can also be used in a clinical setting, for example to allow future patients to practice in home therapy. It operates at low flux of dialysate. The specifications treatments are indicated as follows (Tables 3-4).

Table 3. *Treatment and related parameters.*

	Q_b (ml/min)	Q_{UF} (l/h)	Q_d (ml/min)
HF	0-400	12	0
HDF	0-400	0-12	0-200
HD	0-400	0	0-200
APD	0	0	0-400
UF	0-400	0-2	0

The principle of operation of DIMI is based on the circulation of liquids according to the type of treatment.

There are two treatments which use a semi-permeable membrane: the intracorporeal treatment that uses the peritoneal membrane, and the extracorporeal treatment that requires external circulation of the blood and the use of an artificial membrane.

The circulation of liquids occurs through a sterile disposable device, specially developed and tested to work with the device. To activate the circulation of fluids, the device uses membrane pumps for blood, dialysate and replacement fluid. The waste liquid is controlled by a clamp.

Table 4. *Main technical characteristic of DIMI device.*

Dimension (height, width, depth)	128 cm x 60 cm x 63 cm
Weight	25 kg
Protection Grades IEC 529	IP21
Syringe pump	Yes
Screen	7” touchscreen
Connectivity	Wi-Fi, Bluetooth

The circulation of liquids managed by the system is controlled by pressure sensors that indicate the potential resistance to the flow or the disconnection of the elements, including the patient. Therefore, pressure systems are part of the protections used to ensure patient safety and comfort.

The exchanged volumes are monitored by the pump flows while a scale ensures compliance with the necessary liquid balance. All the exchanged liquids are then taken from the bags placed on the scale or sent towards them. Patient safety is guaranteed by several sensors, such as the ultrasound sensor that detects the presence of possible air bubbles before returning the liquid to the patient, or the colorimetric sensor on the waste liquid that detects potential blood loss or hemolysis. An in-line liquid heater is used to bring the dialysate and replacement liquid close to body temperature. A syringe pump allows you to inject anticoagulants during treatments avoiding anticoagulation. The different components are shown in Figure 3.

Figure 3: *DIMI front view.*

Push/pull hemodiafiltration

Push-pull HDF refers to a hemodialysis setup (without injection of the replacement fluid into the blood) in which the dialysate is injected into the blood through the membrane. This has 2 effects that increase the concentration of solutes in waste substances:

- The volume of the injected dialysate is counterbalanced by an equivalent volume of ultrafiltrate
- The actual flow of dialysate in the dialysate chamber is reduced, with a consequent increase of the blood concentration ratio.

Hemodialysis (HD) remains a standard protocol for the treatment.

Excess water and medium-sized molecules are removed mainly by convention, resulting from the trans-membrane pressure gradient. One of the complications that can occur with hemodialysis is amyloidosis associated with accumulation of larger uremic substances. Hemodiafiltration (HDF) offers the possibility to remove uremic substances of various molecular sizes. It is characterized by a large filtration volume which exceeds the desired removal volume. That said, dehydration needs to be corrected in real time by infusing sterile exogenous replacement fluid. HDF has been reported to provide better dialysis results than high-flow HD, due to better medium and large molecular removal, better control of EPO and inflammation, resulting in lower patient mortality [22].
However, the use of HDF is limited globally since it need infusion of exogenous fluids raising water quality, safety and cost concerns. This has led to modifications of HDF strategies to increase convective mass transfer without the need for exogenous replacement fluid infusion. This is achieved by spontaneous fluid reinfusion at a rate that matches convection. Backfiltration and regenerated ultrafiltrate can be the methods of spontaneous fluid restoration.
Backfiltration is the phenomenon where dialysate moves into the bloodstream across membranes to the area where dialysate pressures are higher than blood hydraulic and osmotic pressures. A pressure drop is inevitable when fluid flows through a cylindrical tube and blood and dialysate pressure decreases along the dialyzers.
Therefore, the TMP, is positive in the proximal region of a dialyzer and the plasma moves into the dialysate compartment through the membranes (forward filtration).
However, fluid movement occurs in the opposite direction in the distal region because the TMP becomes negative and backfiltration occurs, as shown in Figure 4.

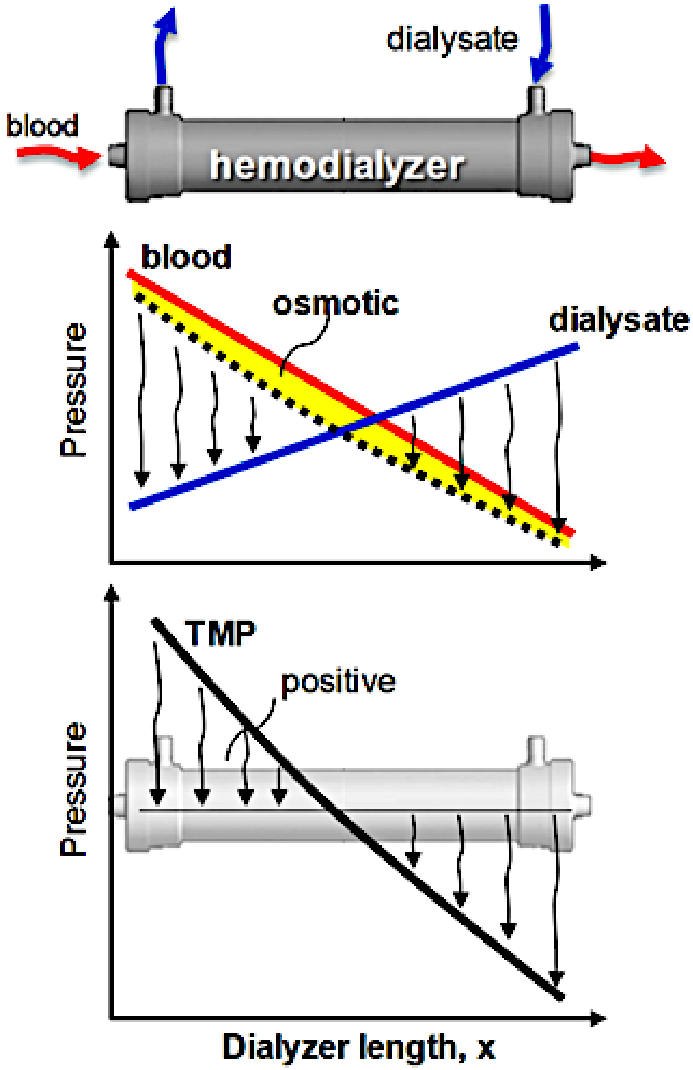

Figure 4. *Backfiltration phenomena.*

Push/pull strategies have also been examined to increase total filtration volumes without the exogenous replacement fluid infusion. The push/pull technique uses the entire membrane as the forward filtration domain for a period of time. However, backfiltration must accompany the forward filtration to compensate for the fluid depletion that occurred due to the forward filtration, and as a result, making it necessary to switch the membranes to a backfiltration domain. In other words, push/pull systems rely on alternate repetitions of forward and backward filtration during dialysis treatment, and the repetitive filtration contributes to the increased total filtration volume.

As several studies report, push/pull HDF leads to an increase of clearance in the same condition with respect to standard hemodialysis. The same studies have shown also an elevated removal rate of middle molecules and reduction of dialysis-related amyloidosis symptoms like back and shoulder pain, restless leg syndrome, and carpal tunnel syndrome. [21, 22, 23, 24]

DIMI has been developed to carry out push/pull HDF in two different ways:

- Dialysate pump it is a membrane pump, which takes the dialysate from the bag in the first stage, and in the second stage the dialyzer is filled up with it;
- Waste substances are handled by a clamp that can be opened or closed.

The four stage of DIMI push/pull HDF are described in the Table 5 and shown in the Figure 5.

***Table 5**. DIMI push/pull HDF*

Dialysate pump	**Waste substance clamp**	**Results in the dialyzer**
No ignition	Closed	Osmosis between blood and dialysate, equilibrium concentration
Ignition	Closed	Dialysate in the blood. Osmosis between blood and dialysate maintained.
Ignition	Open	The dialysate reaches the respective chamber. It is integrated by the ultrafiltrate thanks to the TMP.
No ignition	Open	The ultrafiltrate pass through the membrane and reaches the waste substances.

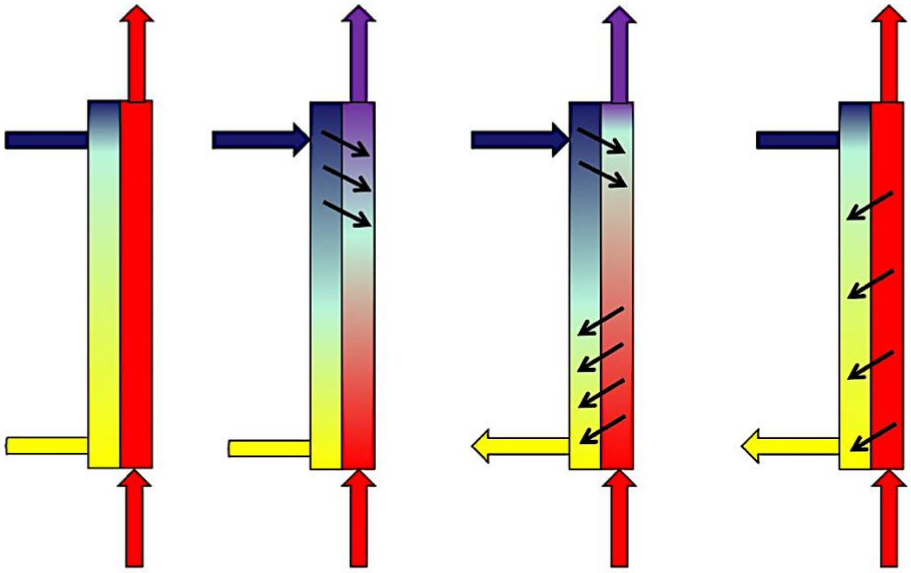

Figure 5. *Four step of DIMI push/pull.*

DIMIBOX

DIMI is a unique intra and extracorporeal blood purification system. It was designed to ensure flexibility and personalization of home care allowing the same system to be used during the various dialysis phases. The easiness to use has largely been considered during the development of the DIMI system.

The transport and installation of the device are facilitated by the foam box to which the machine is screwed and not dedicated electrical circuit is required. Connection to web cloud is an integral part of the device, which can also run without any connection while treatment data are recorded in the machine for a potential later download. User interface is simplified by using many pictograms.

DIMIBOX is a web-based platform connected to the DIMI system developed by Infomed. It has been designed to provide easy, on-demand access to all users, to all DIMI-related data in order to facilitate patient management at home and patient compliance.
It allows definition and revision of therapeutic protocols, monitoring of the treatment progress and viewing the completion of the treatment.

DIMIBOX provides convenient and on-demand access for all users regardless of their geographical location, to all DIMI's related data.

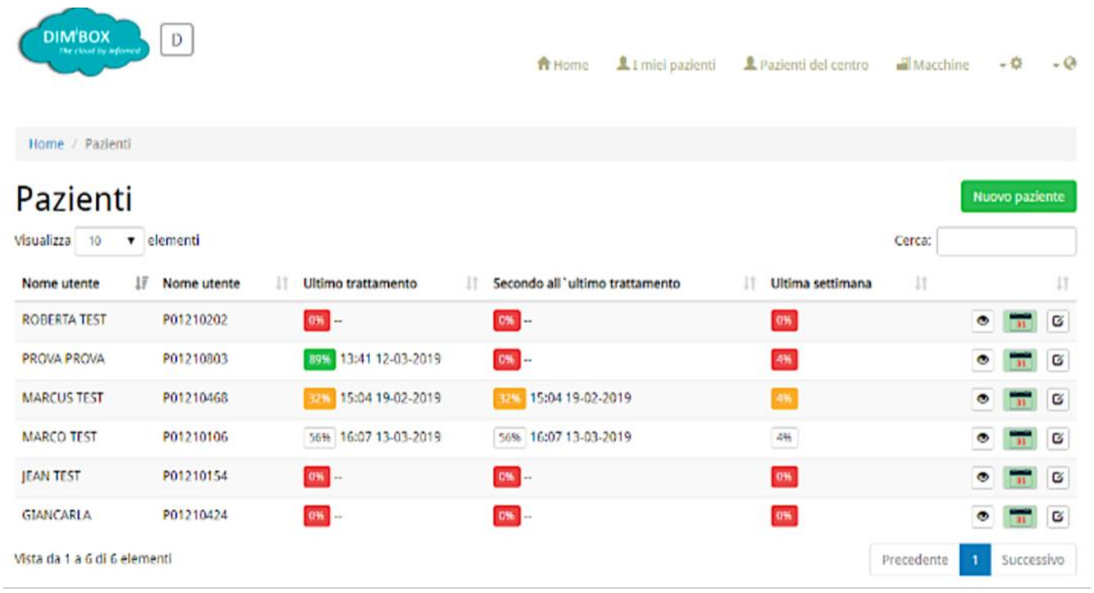

***Figure 6**. Display of processing data in DIMIBOX.*

It allows real-time monitoring of treatments, definition and review of the treatment's protocols and a closer and more efficient relation between stakeholders (Figure 6).
This system allows a strong support to patients providing on-time the right information to the right persons and allows doctors and other health actors (i.e. caregivers) employed in patient management to have visibility on the progress of treatment at home.
As it is analyzed above in the 2.2 chapter, the use of this kind of technologies to remotely monitoring the patient could give more confidence and satisfaction about the care treatment and has the potential to improve therapy outcomes and to confer economic benefits.

Each user has a predefined role and his own login and password to access the platform:

- Doctor: can create patient profile and therapeutic protocol, able to monitor home performance monitoring
- Nurse: only able to view all aspects of treatment
- Technician: license to visualize log and other technical aspect of the machine

- Patient: can observe performed treatments and future planning

Utilizing any web browser, it is possible to access to DIMIBOX with username and password. Doctor with user interface simplified, by using many pictograms, can easily insert a new patient, associate with its nurse, and communicate login credential to the patient.

The ease to use has largely been considered during the development of the DIMIBOX, in fact after entering the dry weight of the patient and the factor, 1,2 default, the system automatically calculates the number of dialysate bags to utilize in a weakly treatment.

Doctor must select the duration treatment (h) and the start date.

The fluid flow (l/h) it is calculated thanks to the algorithm:

$$Q_D = 0.3 \times Q_B \tag{6}$$

The most important aspect of DIMIBOX, related to the fact that the treatment it is performed at home, is the monitoring of treatment data. It is possible to view the summary of the data or visualize it in detail. It also possible to view all alarms during treatment.

Device usage

DIMI uses a small cartridge, which contains all of the blood and fluid circuits, with heating bag included in the disposable. The cassette must be inserted in the cartridge holder, the cassette is the same for all therapies (HF, HDF, PD, UF and HD).

Syringe pump can be used allowing injection of anticoagulation solutions in the blood loop in either a bolus or continuous modes during the whole treatment with the possibility to program a stop of the flow up to 1 hour before the end of the treatment.

Dialysis equipment employs also a low flow lactate or bicarbonate-buffered, ultrapure dialysate, supplied in premixed 5-liter bags. It is possible to install up to 40 l (8 bags) of dialysate/replacement fluid and waste bags offering a new way for long treatment or for patient with a need of large quantity of fluids. An online heater is also used to bring the dialysate and replacement fluid to body temperature; during treatment the heater temperature can be set to 35 °C and 38 °C in increments of 0.1 °C.

The actual temperature of the liquid leaving the heater is controlled by a temperature probe which is displayed on the machine interface during treatment.

The easy use of the DIMI system is possible thanks to several windows that guide the operator in all stage of treatment, thus simplifying the operation. Functioning windows are showed in Figure 7, 8 and 9 in Italian language since for this work DIMI was used in Italian hospital.

When starting the machine, the operator must enter with their personal login credentials:

- Doctors: full access, including prescription
- Nurses: full access, excluding prescription
- Patients: only activation of predefined treatments
- Technicians: can perform in vitro treatment while monitoring the technical parameters.

First of all, if the treatment is just setted the system the patient logs in, the treatment of the day will be proposed based on the existing schedule.

An important parameter, to avoid hypotensive episodes, to be inserted before starting the treatment is the daily weight (with excess of fluid) of the patient before the treatment (W_{eff}, kg), that allows DIMI to calculate at the end of treatment the W_{loss} (kg) that represents the weight loss by the patient during treatment:

$$W_{loss} = W_{eff} - W_{dry} \tag{7}$$

where W_{dry} is the normal weight without any extra fluid in the body.

It is also possible to fill in systolic and diastolic pressure values to monitor patient outcome and avoid systolic hypertensive episodes.

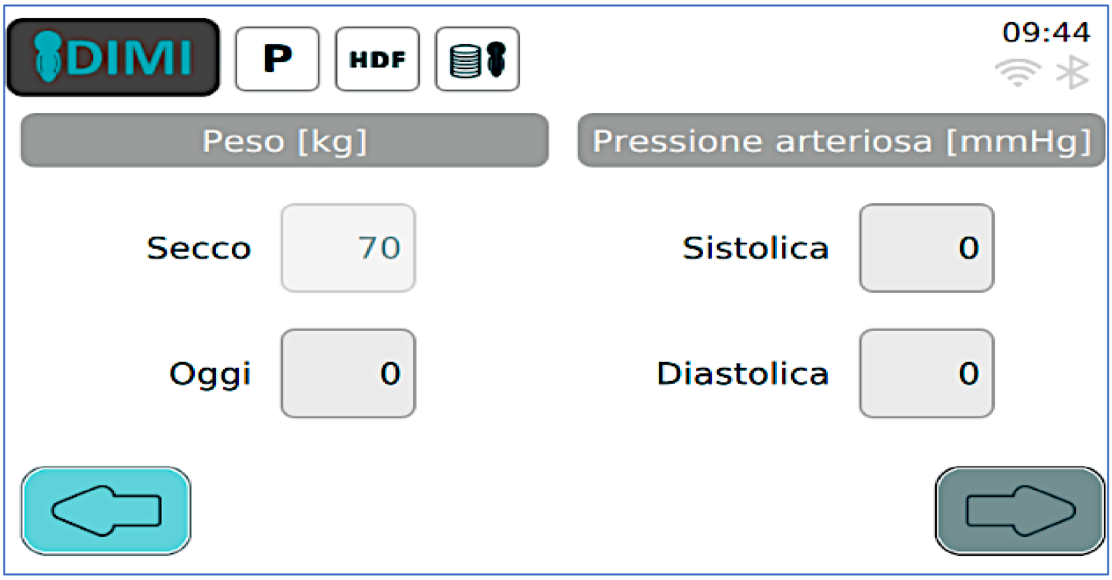

***Figure** 7. Graphic interface to input the patient's weight and pressure values.*

One of the most important innovations provided by DIMI is the possibility to perform at home other renal replacement therapies than hemodialysis and peritoneal dialysis.
This skill makes this machine unique in the reference market offering the possibility to perform for example HDF, one of the most expensive treatment, directly at home avoiding all the problems cited above.

The easy use of the DIMI system is reflected also for these kinds of treatments.
After the doctor, the only able to configure the therapy, has set the therapy, the patient has to insert the login credential corresponding to specific HDF therapy, in which the following parameters are visible (Figure 8):

- Duration
- Dialysate volume
- Ultrafiltration volume.

If anticoagulant is required, the doctor has to press the button to define the syringe to be used during priming and treatment.
The main treatment window (Figure 9) shows the parameters that can be changed or that need to be monitored during treatment. The same windows also display the progression of the treatment and the time remaining to its completion.

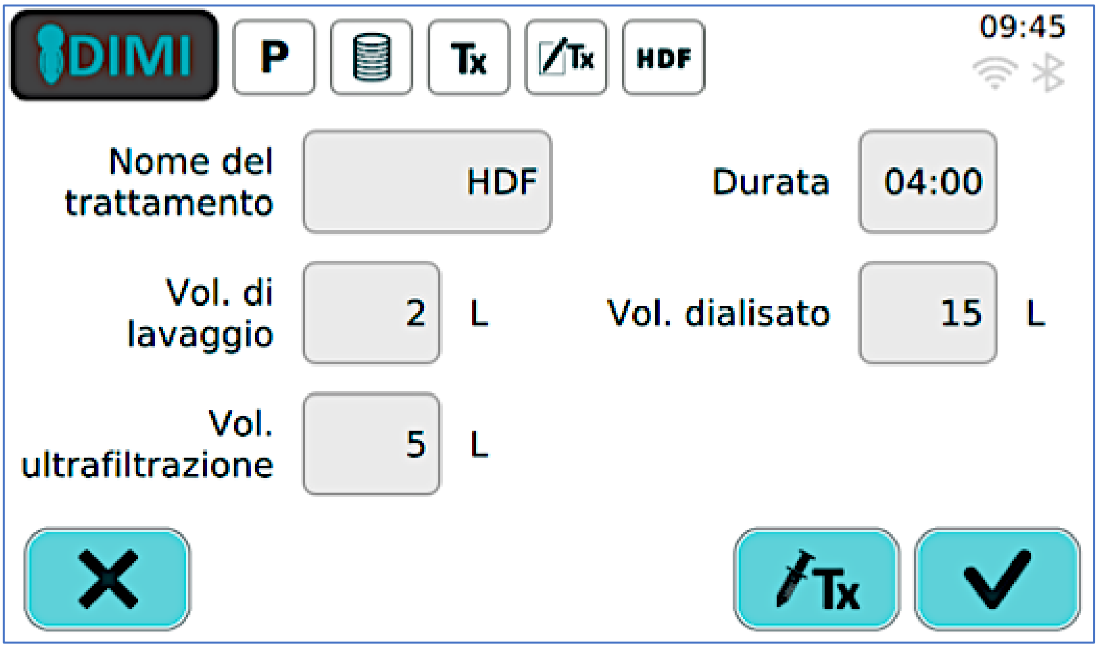

Figure 8: *Graphic window to set the treatment configuration.*

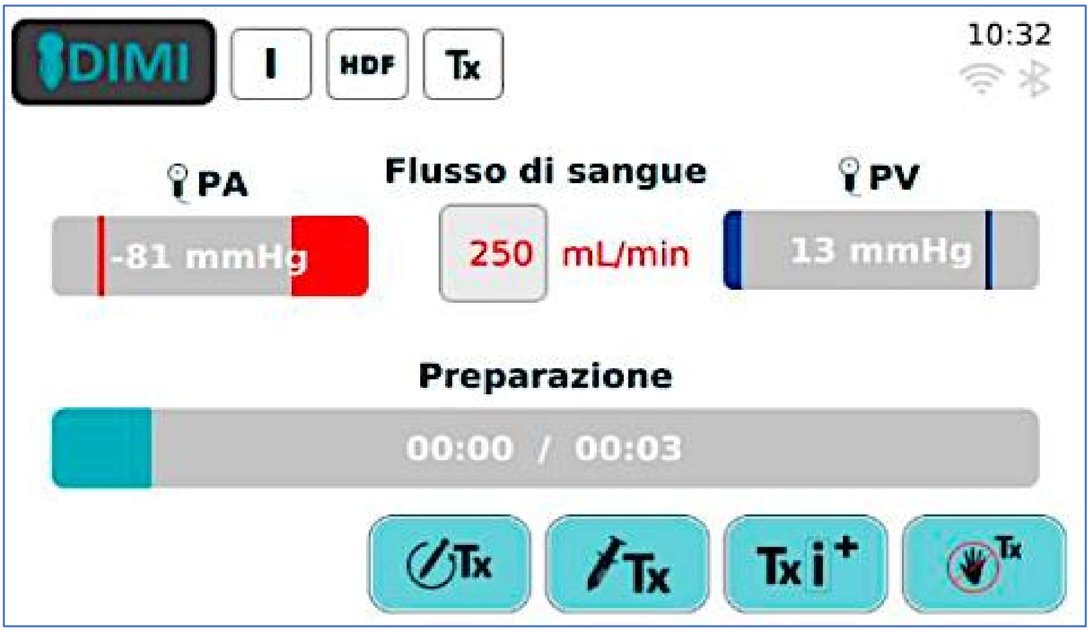

Figure 9: *Graphic window showing the progress of treatment.*

5. Materials and methods

The new DIMI device was used in fourteen prevalent patients affected by kidney failure, aged 68 ± 11 years, in the dialysis unit of the University Hospital of Chieti.

As described before, DIMI is able to perform different treatments: hemodialysis, hemodiafiltration, ultrafiltration, peritoneal dialysis and hemofiltration. DIMI offers the possibility to perform these treatments at home, but in this work it was used in a clinical setting to allow future patients to practice in home therapy.

Before the therapies were started, the doctors set the machine according to the patient's need.

After the patient was attached to the machine through a shunt, the circulation of liquids occurred through a sterile disposable device. The pressure sensors that control the circulation of liquids, indicating the potential resistance to the flow or the disconnection of the elements, did not detect any disconnection during each session.

Eleven patients underwent a session of hemodialysis with a lactate-based dialysate volume of 20 liters, using a high-flux polyethersulfone hemodialyzer (Dimysis 017, Infomed). Two further patients underwent an HD session of 4 hours and another one an HD session of 3 hours.

For patients undergoing HD, the DIMI treatment specifications given in Table 6 were used:

Table 6: *Treatment parameters used in eleven HD patients, Q_d was calculated trough equation (6).*

	Q_b (ml/min)	Q_d (ml/min)
HD	0-250	0-75

As previously mentioned, DIMI offers the possibility to perform at home other renal replacement therapies than hemodialysis and peritoneal dialysis, such as HDF, one of the most expansive treatment. This thanks to the push/pull technique able to avoid all problems concerning the standard HDF technique such as necessity to infuse a sterile liquid and backfiltration.

In this work only one patient underwent a HDF session of 2.5 hours. The following Table 7 shows the treatment parameters ranges used in HDF treatment:

Table 7: Parameters treatment for HDF patient, Q_d was calculated trough the equation (6)

	Q_b (ml/min)	Q_{UF} (l/h)	Q_d (ml/min)
HDF	0-400	0-12	0-200

In this study for each patient, before and 15 minutes after the extracorporeal procedure the following parameters, to assess the adequacy of treatment, are measured:

- Blood Urea Nitrogen (BUN),
- Creatinine,
- Potassium,
- Sodium,
- Calcium,
- Lactate,
- pH,
- Kt/V.

Blood urea nitrogen (BUN) is a medical test that measures the amount of urea nitrogen found in blood. The liver produces urea in the urea cycle as a waste product of the digestion of protein. BUN levels are inversely correlated with the decline of kidney function. In general, normal BUN levels fall in the following ranges: adult men 8 to 24 mg/dL, adult women: 6 to 21 mg/dL.

Creatinine is a chemical waste product that is released into the blood when muscles contract. When kidney function is normal, creatinine is filtered from the blood through the kidneys. When creatinine levels are high, it can be an indicator of kidney disease. It has been estimated that 2% of the body's creatine is converted into creatinine every day, resulting in the daily generation of creatinine at a fairly constant rate (male: 20 to 25 mg/kg/day; female 15 to 20 mg/kg/day). Its elevated level in blood indicates kidney disease (up to 1.4 mg/dl).
Electrolytes are particles that carry an electric charge when they are dissolved in blood. The kidneys help to regulating electrolytes concentrations in the body. Any disturbance in this process often leads to an electrolyte imbalance.

The electrolytes taken from blood chemistry in the population considered for this study are:

- Sodium
- Potassium
- Calcium

Potassium is the most abundant cation in the body. The vast majority of potassium is in the intracellular compartment with a small amount in the extracellular space. For people with stage 5 CKD (also known as end stage renal disease), dialysis is necessary to help regulate potassium. Between dialysis treatments, however, potassium levels rise, and high-potassium foods must be limited. Normal serum potassium is 3.5 to 5.5 (mEq/L).

Sodium is a substance needed by our body to work normally. In fact, it helps make sure that nerves and muscles work properly. Sodium is also important because it helps maintain the right balance of fluids in the body. The kidneys help keep sodium at a healthy level. A normal blood sodium level is between 135 and 145 (mEq/L). When sodium level rises up to normal range, kidneys cannot remove enough of it and leads to hypernatremia. Instead, too little concentration of sodium in the blood leads to hyponatremia.

Calcium it is essential for the proper functioning of muscles, nerves, and the heart and is required in blood clotting and in the formation of bones. About 99% of calcium is found in the bones while the remaining 1% circulates in the blood. Some calcium is lost from the body every day, filtered from the blood by the kidneys and excreted into the urine. Measurement of the amount of calcium in the urine is used to determine how much calcium is being eliminated by the kidneys. The body is set to have a normal amount of calcium (somewhere between 8.6 to 10.3 mg/dL). When calcium level rises up to normal range leads to hypercalcemia. Instead, too low concentration of calcium leads to hypocalcemia.

In regulating blood bicarbonate concentration, the kidneys play a central role in acid-base homeostasis (7.35-7.45), and severe renal failure causes metabolic acidosis. Controlling blood pH in individuals suffering from severe acute kidney injury (AKI) and undergoing renal replacement therapy is of paramount importance in critical care settings.

URR refers to the treatment-related reduction of serum urea concentration. URR is a simple but rather imprecise way to quantify dialysis dose because it does not take into account intradialytic urea generation and convective urea removal by ultrafiltration. Despite these limitations, URR correlates well with dialysis outcome and is an accepted method for assessment of dialysis adequacy. A minimum URR of 65% to 70% is recommended for adequate HD. In this thesis URR was calculated as follow:

$$\mathrm{URR} = \frac{\mathrm{U_{pre}} - \mathrm{U_{post}}}{\mathrm{U_{pre}}} \tag{8}$$

Kt/V is another way of measuring dialysis adequacy. However, though imperfect, it remains to-date the most widely used measure. One must remember to assess the patient on multiple parameters including symptoms of uremia, volume status, electrolytes, nutritional status, and not just rely on Kt/V to make changes to any dialysis prescription. Despite of this in literature was found the limit of usage Kt/V as the sole criterion of adequacy [25]. The target Kt/V for 3 times a week in-center hemodialysis is about 1.2 to 1.4. Three weekly treatments with a single pool Kt/V would provide a weekly standard Kt/V of about 2.0. In home hemodialysis, as the number of sessions per week are higher, the target per session Kt/V is lower, around 0.5 to 0.6, depending on the number of sessions per week, to achieve a weekly standard Kt/V of 2 to 2.2.
All the parameters described above have to decrease and fall in their normal ranges according with the literature, considering the execution of only one treatment [26, 27, 28, 29, 30].

5.1 Statistics

For patients that show more than one blood chemistry tests an average of the parameters has been computed.
The data were submitted to the Lilliefors normality test to reveal a normal distribution of the data (pre- and post-DIMI treatment).

Next to determine which groups are significantly different, if the normality test tells that both groups to be compared (i.e. BUN pre and BUN post) are normal, the ttest2 was applied, otherwise, if only one of the two is not normal, the Wilcoxon rank sum test was applied. The significance level was set at 5% for all tests.
Percentual variation has been calculated between for all pre- and post-treatments data that showed significant difference.

6. Results

In each patient blood parameters were measured by standard laboratory techniques before and 15 minutes after the extracorporeal procedure.

The following Table 8 reports blood parameters measured before DIMI treatment: BUN (mg/dl), Creatinine (mg/dl), Lactate (mmol/l) Potassium (mEq/l), Sodium (mEq/l), Calcium (mg/dl) and Ph. The same table also reports gender (M= male, F=female), age (years), duration of treatment (hours) and kind of treatment of each patient (P). Missing data are indicated with slash (/).

Table 8. *Blood parameters measured before the DIMI treatments*

P	Gender	Age	Treatment	Duration (hours)	BUN (mg/dl)	Creatinine (mg/dl)	Lactate (mmol/l)	Potassium (mEq/l)	Sodium (mEq/l)	Calcium (mg/dl)	Ph
1	M	56	HD	2.5	66	12.88	1.26	4.99	138	7.16	7.401
2	F	/	HD	2.5	57	16.64	1.55	9.07	139	7.68	7.361
3	F	65	HD	2.5	/	/	1.65	4.77	137	9.12	7.322
4	M	/	HD	2.5	61	8.95	1.31	6.31	139	1.14	7.298
5	F	/	HD	2.5	80	3.85	1.22	4.69	143	8.64	7.378
6	M	/	HD	2.5	67	12.88	3.11	6.26	122	8.08	7.195
7	M	/	HD	2.5	36	6.13	0.91	5.02	140	9.21	7.437
8	F	60	HD	2.5	62	8.47	1.29	4.19	140	8.96	7.413
9	M	/	HD	2.5	43	6.88	1.28	4.91	135	9.36	7.443
10	F	70	HD	2.5	64	6.23	1.28	3.51	137	8	7.371
11	M	69	HDF	2.5	174	10.72	/	4.91	141	9	/
12	F	83	HD	4	/	/	/	/	/	/	/
13	M	84	HD	4	/	/	/	/	/	/	/
14	M	56	HD	3	163	10.13	1	5.68	136	9.2	7.277

Table 9 shows calculation of URR (%) and Kt/V for each patient. Lacking data are identified with slash symbol. Mean and standard deviation are reported as well.

Table 9. *URR and Kt/V measured post DIMI treatment*

PATIENT	URR (%)	Kt/V
1	43.7	0.64
2	38.8	0.51
3	/	/
4	39.9	0.54
5	42.7	0.62
6	48.2	0.76
7	27.5	0.22
8	42.7	0.61
9	41.7	0.59
10	40.4	0.56
11	/	/
12	/	/
13	/	/
14	44.78	/
Mean ± SD	42 ± 5	0.6 ± 0.2

The Table 10 below reports blood parameters measured 15 minutes after DIMI treatment: again, missing data are denoted by a slash (/).

Table 10. *Blood parameters measured after the DIMI treatment.*

P	Gender	Age	Treatment	Duration (hours)	BUN (mg/dl)	Creatinine (mg/dl)	Lactate (mmol/l)	Potassium (mEq/l)	Sodium (mEq/l)	Calcium (mg/dl)	Ph
1	M	56	HD	2.5	37	7.93	3.51	3.35	140	7.46	7.458
2	F	/	HD	2.5	35	4.83	8.35	3.30	138	8.62	7.393
3	F	65	HD	2.5	/	/	6.27	3.77	137.9	9.04	7.338

4	M	/	HD	2.5	37	5.48	9.71	4.24	139	1.12	7.34
5	F	/	HD	2.5	46	2.73	8.31	3.36	142	8.72	7.411
6	M	/	HD	2.5	46	7.19	14.2	3.87	140	8.72	7.262
7	M	/	HD	2.5	46	4.27	4.35	3.89	141.4	9.24	7.427
8	F	60	HD	2.5	46	3.92	6	3.1	138	9.18	7.456
9	M	/	HD	2.5	25	4.25	9.87	3.77	136.7	9.44	7.477
10	F	70	HD	2.5	38	3.71	1.28	3.33	138	9.2	7.38
11	M	69	HDF	2.5	151	9.85	/	4.7	140	8.9	/
12	F	83	HD	4	/	/	/	/	/	/	/
13	M	84	HD	4	/	/	/	/	/	/	/
14	M	56	HD	3	90	5.01	3.31	3.21	136	8.2	7.361

The following Figure 10 introduces the average value (± standard deviation, SD) of the BUN mg/dl) index (mg/dl) before (left column) and after (right column) a DIMI session. As described in Table 8, the average values have been computed over a population of 11 patients only, since BUN data in patients 3, 12, and 13 is lacking. A significant ($p < 0.05$) 38.5 % reduction of BUN index is detected after DIMI treatment. Comparable inter-patient variability of BUN values before and after treatment, quantified by SD values, is detected.

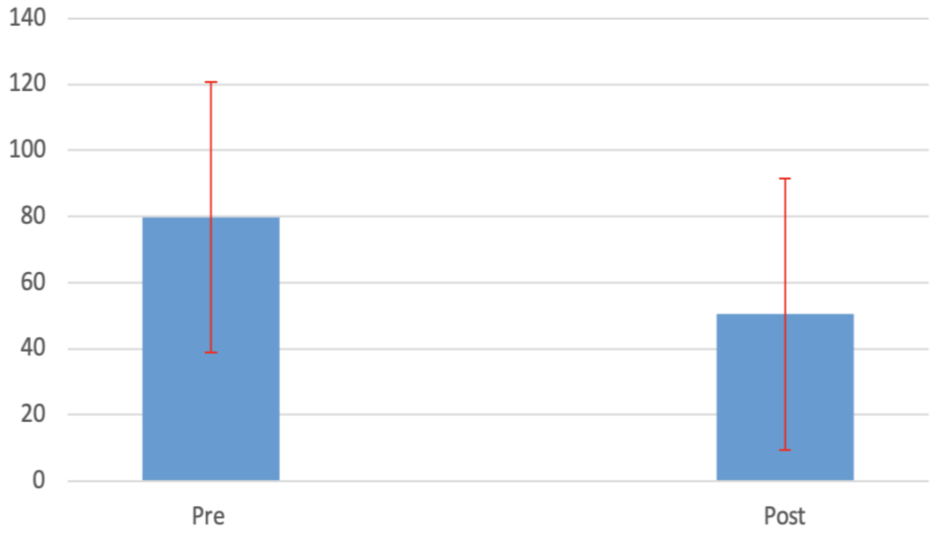

Figure 10. *BUN mean and standard variation before (Pre, left) and after (Post, right) session with DIMI.*

The Figure 11 below shows the average value (± standard deviation, SD) of creatinine (mg/dl) index before (left column) and after (right column) DIMI treatment. Again, the average values have been computed over a population of 11 patients, since creatinine data in patients 3, 12, and 13 is lacking. A significant ($p < 0.05$) 37.5 % reduction of creatinine index is detected after DIMI treatment. Comparable inter-patient variability of creatinine values before and after treatment, quantified by SD values, is detected.

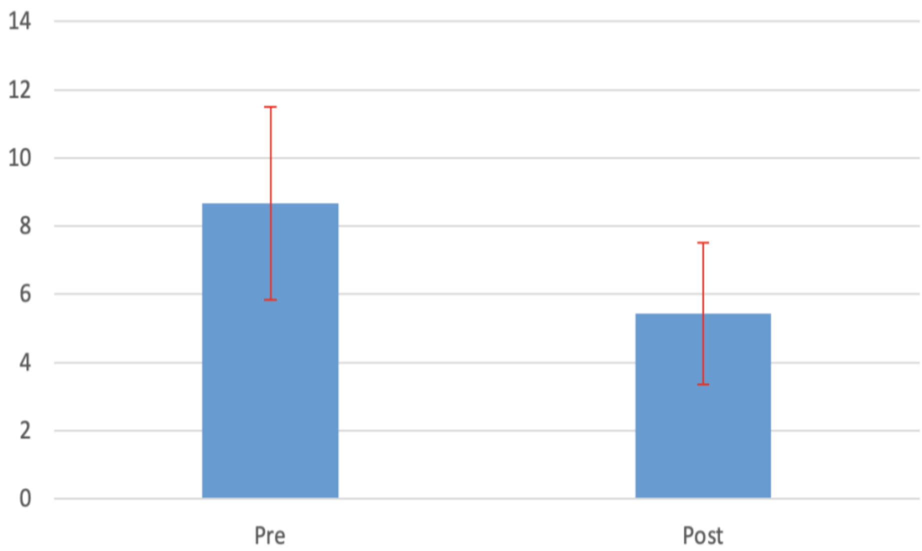

Figure 11. *Creatinine mean and standard variation before (Pre, left) and after (Post, right) session with DIMI*

Figure 12 evidences the average value (± standard deviation, SD) of potassium (mEq/l) index before (left column) and after (right column) DIMI session. As for the creatinine data the average values have been computed for all patients except for patient 12, and 13 in which the potassium data lack. A significant ($p < 0.05$) 25.5 % reduction of creatinine index is detected after DIMI treatment. Comparable inter-patient variability of creatinine values before and after treatment, quantified by SD values, is detected.

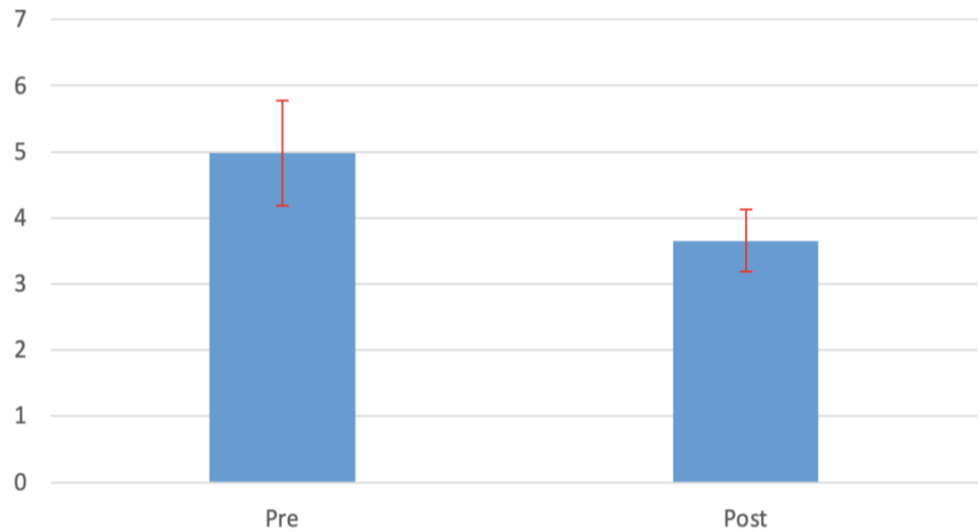

Figure 12. *Potassium mean and standard variation before (Pre, left) and after (Post, right) session with DIMI*

In the following Figure 13, the average value (± standard deviation, SD) of Ph, a dimensionless parameter, before (left column) and after (right column) DIMI session is reported. From Table 8, it can be argued that average values have been computed for all patients except for patient 12, and 13 and for the patient 11 (HDF treatment). A significant ($p < 0.05$) 0.5 % reduction of Ph index is detected after DIMI treatment. Comparable inter-patient variability of creatinine values before and after treatment, quantified by SD values, is detected.

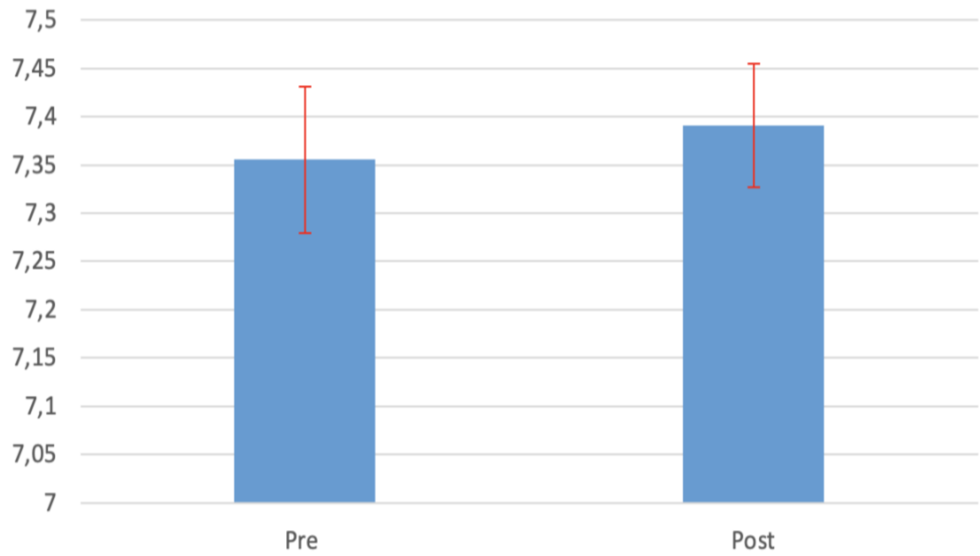

Figure 13. *Ph mean and standard variation before (Pre, left) and after (Post, right) session with DIMI*

In the following Figures 14-17, the variation of those parameters that have exhibited a significant difference (pre and post DIMI session) in each patient is provided. To understand better and highlight the variation, a red line, reporting the percentage variation, is superimposed to histograms. Variation was expressed as a positive percentage and represents how the parameter has decreased for a given patient. In the y-axis on the left side of the graph, a scale relative to the unit of measure of the parameter's concentration was setted, instead in the y-axis on the right side, the percentage variation scale has been used. The x-axis reports the patient identification number, to which the parameters in Table 8 and 10 (pre and post DIMI session respectively) correspond.

In particular, the following Figure 14 shows the value of the BUN index before (blue column) and after (orange column) DIMI session for each patient. The BUN variation for each patient has been indicated with a red line reporting also its percent value. After DIMI treatments BUN values decrease on average by 38 %, with the highest variation detected in the patient 6. Only 18% of the patients fall in the pre-treatment BUN range between 81-180 mg/dl. Most of the patients have pre-treatment BUN level between 20-80 mg/dl (82 %). A high BUN variation among pre- and post-treatment was estimated in the patient 14. After DIMI treatment most of the patients (73%) have a BUN level in the range 20-40 mg/dl, and only 27% of them exhibit a BUN in the range 40-160 mg/dl.

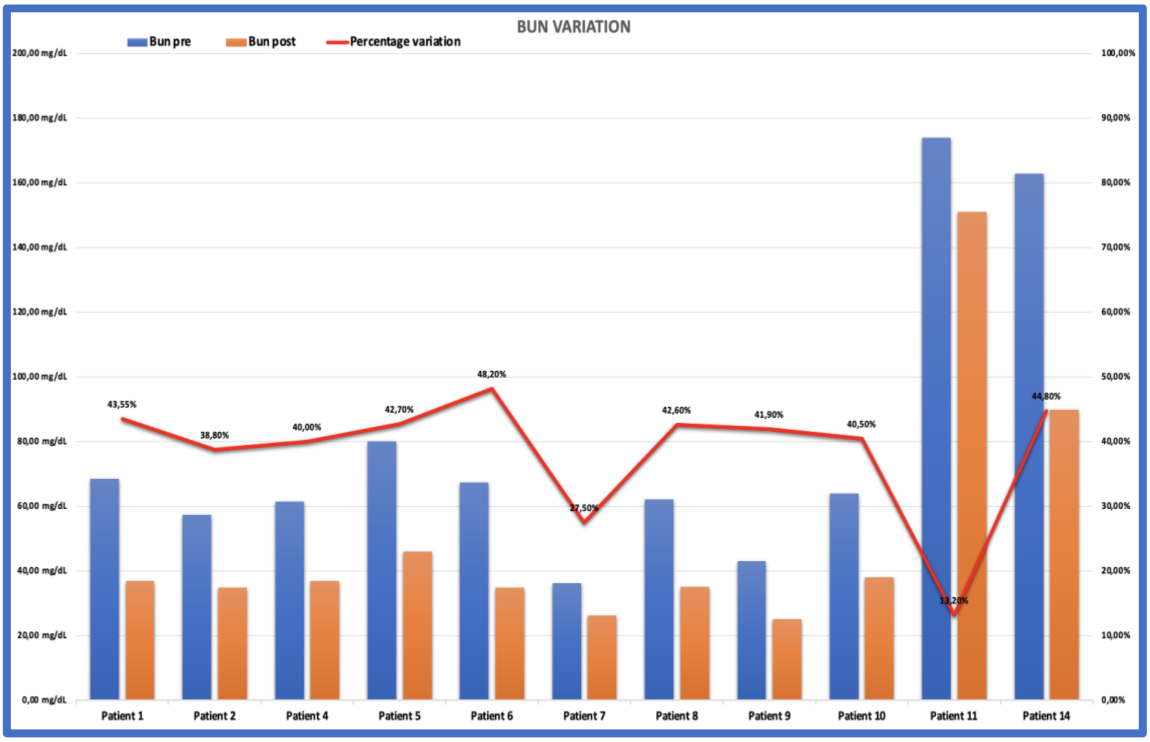

***Figure 14**. BUN variation (red line) with respect to pre-treatment BUN (blue columns) and post-treatments BUN (orange columns), for each patient.*

Figure 15 shows the variation of creatinine concentration (mg/dl) before (blue column) and after (orange column) DIMI session. Creatinine variation for each patient has been indicated with a red line reporting also the percent value of creatinine index variation after DIMI treatment. Most of the patients have a serum creatinine level between 7,5-14 mg/dl (78%) and 3-7 mg/dl (22%) before dialysis. After DIMI treatments, creatinine values decrease on average by 37.5%), with the best variation measured for patient 14 (50.5 %). Patient 1 and 6 that show high pre-treatment creatinine concentration exhibit high variation, respectively 38.1 % and 40.8 %. Lower variation of 3.9 % can be noticed for patient 8. After DIMI treatment most of the patients (73 %) have a creatinine level in the range 2-6 mg/dl, and only 27 % of the population exhibits an index in the range 6-10 mg/dl.

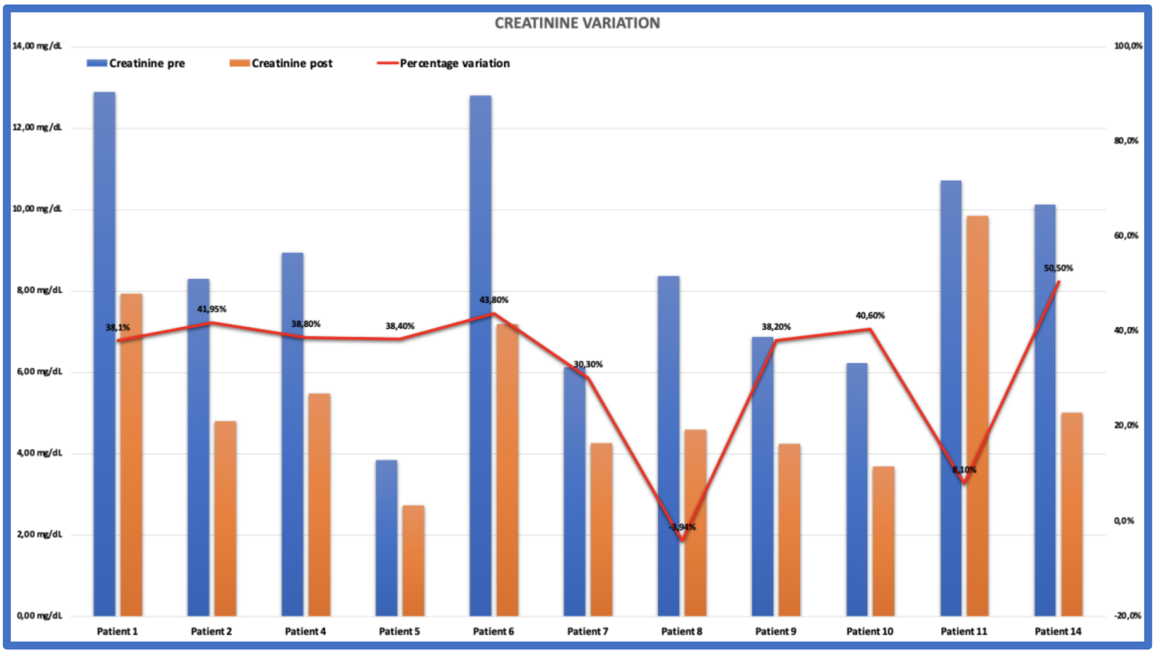

***Figure 15**. Creatinine variation (red line) with respect to pre-treatment Creatinine (blue columns) and post-treatment Creatinine (orange columns), for each patient.*

The variation of potassium concentration (mEq/l) before (blue column) and after (orange column) DIMI session is shown in Figure 16. Potassium variation for each patient has been indicated with a red line reporting also its percent value. Most of the patients show a Potassium level between 4-5 mEq/l (66 %), and 5-7 mEq/l (25 %) before dialysis. After DIMI treatments, the Potassium values decrease on average by 25 %, and the best variation was found in patient 14 (43.5 %). Patients 4 and 6 featuring high pre-treatment Potassium concentration exhibit high variation, respectively 32.7 % and 38.2 %. A lower variation of 4.1 % can be observed for patient 11. After DIMI treatment most of the patients (84 %) have a Potassium level in the range 1-3.9 mEq/l, while only 16 % of the population falls in the range 4-5 mEq/l.

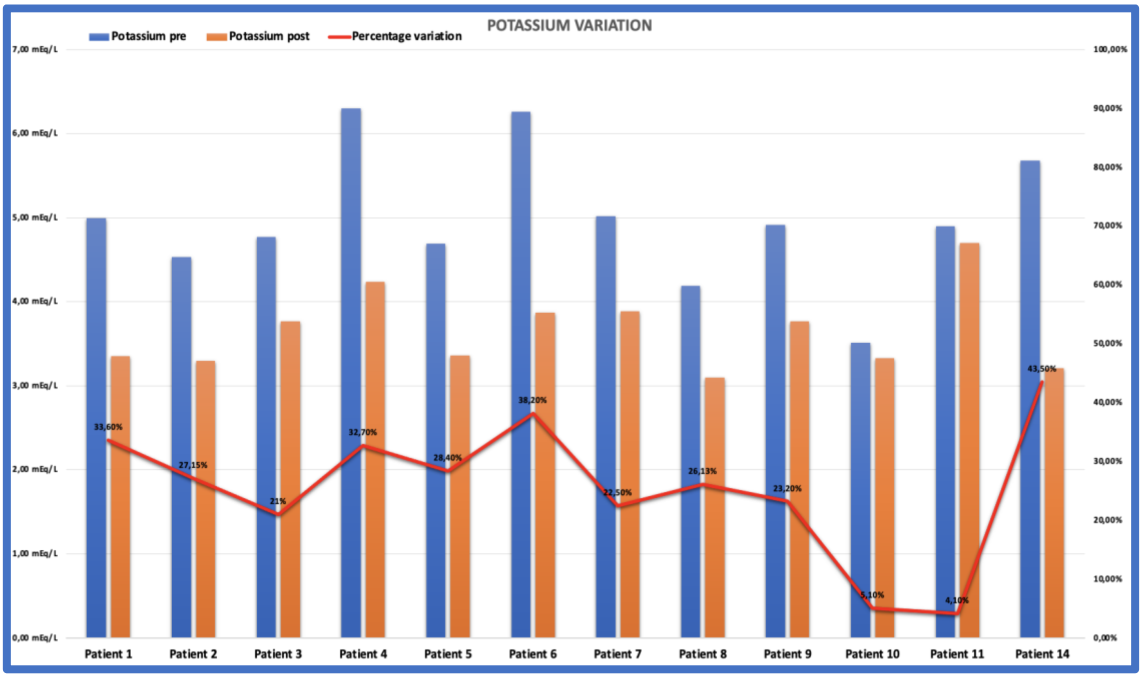

Figure 16. *Potassium variation (red line) with respect to pre-treatment Potassium (blue columns) and post-treatment Potassium (orange columns) for each patient.*

Finally, in the same fashion as before, Figure 17 shows the variation of Ph before (blue column) and after (orange column) DIMI session. Most of the patients show a Ph level between 7.35-7.5 (66 %), 16% of them are in the range 7.2-7.3 before dialysis. After DIMI treatments, the Ph values change on average by 0.5 %, with the best variation measured in the patient 14 (1.2 %). A lower variation of 0.1 % can be observed in the patients 7 and 10.

It is important to point out that the variation of Ph determined by the DIMI treatment is unsensitive to the initial value of the Ph index before the treatment and, differently from what can be observed for the other indexes, the percent variation is quite stable all over the different patients.

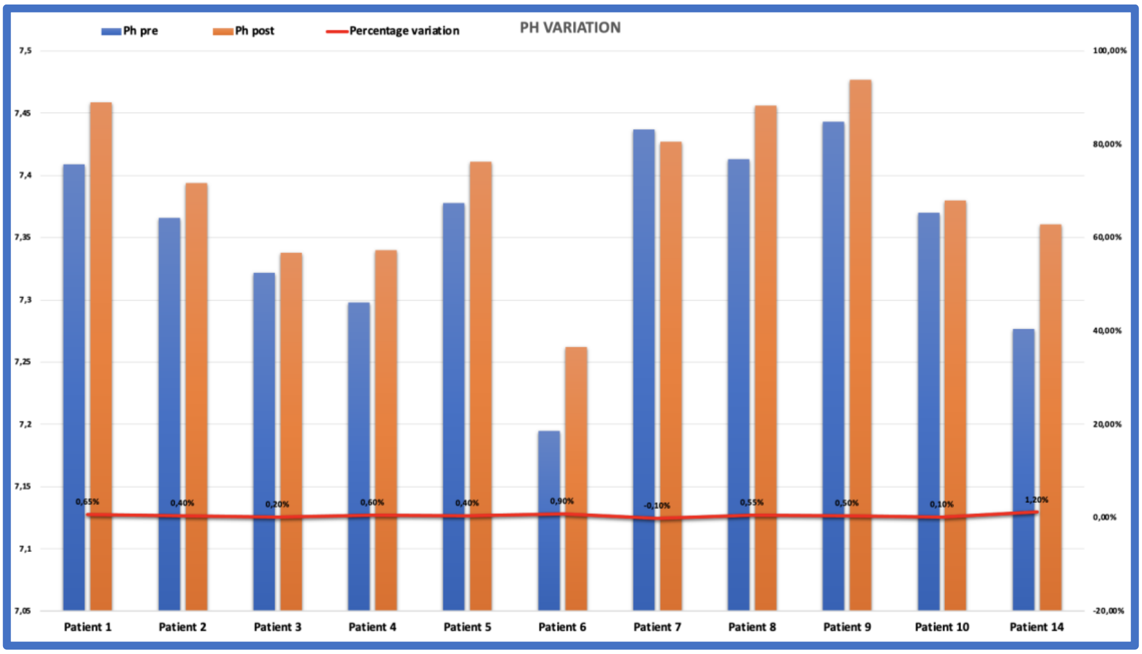

Figure 17. *Ph variation (red line) with respect to pre-treatment Ph (blue columns) and post-treatment Ph (orange columns), for each patient.*

7. Discussion and conclusion

Renal replacement therapy is a precious, irreplaceable and indispensable asset for the treatment of numerous pathological conditions of kidney disease [9]. Dialysis and blood purification represent lifesaving therapies before the renal replacement therapy [12].

The aim of this work was to carry out an evaluation of home hemodialysis treatment evaluating variation in parameters considered as markers of dialysis adequacy. To this aim, the newest DIMI blood purification device, developed by Infomed and able to perform at home all treatments related to the kidney disease, was used. For this study fourteen prevalent patients (68 ± 11 years) with kidney failure have been subject to DIMI treatment sessions of HD and HDF in the dialysis unit of the University Hospital of Chieti. The DIMI machine, even if designed to target home applications, was used in a clinical setting to allow future patients to practice in home therapy. In each patient, before and 15 minutes after the extracorporeal procedure the following parameters, to assess the adequacy of treatment, were measured: blood urea nitrogen (BUN), Creatinine, Potassium, Sodium, Calcium, Lactate, pH, Kt/V. Also, URR was calculated.

Results (Figures 10, 11, 12) show parameters with a significant variation, between pre- and post-DIMI treatment, expressed as mean and standard variation before and after the extracorporeal session with DIMI. In the Figure 13 is also reported the variation of Ph although it did not express significant differences among the patients. The average decrease in concentration of BUN, Creatinine, Potassium and Ph were of 38.5 %, 37.5%, 25.5 % and 0.5% respectively. Decreases in these parameters concentration are in accordance with the literature considering the execution of only one treatment [26, 27, 28, 29, 30], thus evidencing the potential benefit associated to the use of the DIMI device. In particular Figure 13 shows how Ph remains stable after the DIMI treatment and according to the fact that not significant differences for pre- and post-DIMI treatment were expressed, it underlines the fact that one of the fundamental goals in blood purification treatments, i.e. to maintain the Ph value stable, can be reached by the DIMI-based treatment.

Results from Figure 14 show the BUN variation in relation to each patient. In general, normal BUN levels fall in the following ranges: adult men 8 to 24 mg/dl, adult women 6 to 21 mg/dl. In this study all patients initially show a BUN value higher than normal range. In particular patients 11 (HDF treatment) and 14 exhibit 174 mg/dl and 163 mg/dl, respectively. According to the literature, BUN after hemodialysis has to decrease [26]. Following the DIMI treatments, BUN values decrease on average by 38 %, the highest variation was estimated in the patient 6 (male subject). Despite the higher concentration of BUN, also in patients 11 and 14 the values decrease (Figure 14). In fact, after DIMI treatment, most of the patients (73%) have a BUN level in the range 20-40 mg/dl, and only 27% in the range 40-160 mg/dl. Wilcoxon rank sum test shows significative difference between pre- and post-BUN levels. So, it evidences the fact that DIMI sessions lead to a positive decrease of BUN concentration how it occurs in the literature [26].

Figure 15 reports Creatinine variation in relation to each patient. Creatinine is produced from muscles and is excreted through the kidneys. It has been estimated that 2% of the body's creatine is converted into creatinine every day, resulting in the daily generation of creatinine at a fairly constant rate (male: 20 to 25 mg/kg/day; female 15 to 20 mg/kg/day). Its elevated level in blood indicates kidney disease (up to 1.4 mg/dl) [27].

Most of the patients have a serum creatinine level between 7,5-14 mg/dl (78 %) and 3-7 mg/dl (22 %) before dialysis (Figure 15). DIMI has a positive impact on reducing the serum creatinine level. Results showed that most of the patients (86%) had serum creatinine below 76 mg/dl after dialysis (Fig. 17)

In this study according with the literature [27] the creatinine levels decrease after treatment.

In particularly:

- Ttest2 shows significative difference between pre- and post-creatinine levels.
- The best variation was estimated in patient 14.
- The patient who underwent HDF (patient 11) also shows decreased creatine concentration.

Figure 16 shows how Potassium concentration varies after treatment with respect to before treatment. Potassium is the most abundant cation in the body. The vast majority of potassium is in the intracellular compartment with a small amount in the extracellular space. Normal serum potassium is 3.5 to 5.5 mEq/l. Total body potassium is usually lower in females and in older patients.

Figure 16 shows that:

- Male patients show higher level of serum potassium (in particular patients 4, 6 and 14) with respect to female ones.
- All patients show decreased level of potassium 15 minutes after DIMI treatment (Figure 18).
- The best variation is for the patient 14.
- HDF patient (11) shows a decrease of 4,10 %.
- Ttest2 shows significative difference between pre- and post-potassium levels.

Most of the patients show Potassium level between 4-5 mEq/l (66 %), 5-7 mEq/l (25 %) before dialysis. After DIMI treatments Potassium values decrease (on average by 25 %). So, the significative difference evaluated by the Ttest2 and effective decrease of potassium level during the course of treatment as reported in literature [28], enhance the positive effect of DIMI treatment.

In regulating blood bicarbonate concentration, the kidneys play a central role in acid-base homeostasis (7.35-7.45), and severe renal failure causes metabolic acidosis [29].

Figure 19 shows:

- In all patients the Ph remains relatively stable (0.49% mean variation)
- Ttest2 does not show significant difference between Ph pre- and post-DIMI treatment.

So, these results are in accordance with the fact that one of the fundamental aspects in blood purification treatments is to maintain the Ph value stable.

Table 9 reports calculation of URR (%) and Kt/V for each patient except for patients 3, 12, 13 since data is lacking. URR refers to the treatment-related reduction of serum urea concentration. URR was calculated trough the formula (8) 15 after DIMI session. From literature it is evident that URR correlates well with dialysis outcome and is an accepted method for assessment of dialysis adequacy [30]. A minimum URR of 65% to 70% is recommended for adequate HD [30]. In this study, the URR was 42 % ± 5 % (average value ± SD) after only one session of treatment.

Kt/V is another way of measuring dialysis adequacy. The target Kt/V for 3 times a week in-center hemodialysis is about 1.2 to 1.4. Instead, for home hemodialysis it is around 0.5 to 0.6, depending on the number of sessions per week, since the number of sessions per week are higher. In this study, the Kt/V was 0.6 ± 0.2 (average value ± SD) after only one session of DIMI treatment.

Despite of their importance, it was analyzed that performing dialysis treatments in hospital causes high impact on the Italian National Health Service (NHS), estimated to be € 2.1 billion per year [2]. For what concerns hemodialysis, in general treatments are performed in hospital or CAL, usually 3 times per week for about 3-4 hours at a time. Instead, peritoneal dialysis is performed usually at home for 3-5 exchanges at day, but only 40% of patients are candidate for this kind of therapy [5]. Furthermore, several studies report that applying approaches in which the patient carries out the therapy without moving into the hospital or care facility, and in which the patient can choose the time of day to perform dialysis, guarantees more freedom in dailylife and better compliance by the patient. For this reason, patients often feel better, both emotionally and physically, switching from in center to home dialysis [8, 9, 10]. Nowadays, especially due to the of lockdown imposed by the COVID-19 pandemic it is evident how the fundamental objective of chronic care systems is to keep the sick person at home as much as possible [1].

Home hemodialysis, how it is discussed in this work, represents a real alternative to focus the therapies at home offering significant advantages in terms of clinical results, socio-economic savings and quality of life of the patient. The newest home hemodialysis machines designed to take up less space and to require fewer supplies have helped to increase the focus on territorial medicine.

For what concerns hemofiltration, hemodiafiltration and ultrafiltration, that are suitable for all patients with multiple organs disfunction, in literature they are reported as high-cost therapies due to their own characteristics [31]. These therapies are performed usually in intensive care units, and in the market there are alternative devices to perform them at home. From the data acquired on 14 patients extracorporeal session with the new DIMI device shows significative decrease in concentration of parameters correlated with the dialysis adequacy. Data of the patient 11 who underwent hemodiafiltration shows decreased levels of BUN, Creatinine, and Potassium. In particular, for the Ph results, it shows not significant difference for pre- and post-DIMI treatment, in accordance with the fact that one of the fundamental goals in blood purification treatments is to maintain the

Ph value stable. In the population of 14 patients who underwent DIMI treatment in the Hospital of Chieti, the same variation of the blood-related parameters as present in the literature has been evidenced. Results related to the patient that underwent the DIMI hemodiafiltration treatment confirm the positive applicability of this device also for this kind of treatment.

In fact, in relation to the above, nowadays in the market several devices to develop hemodialysis and peritoneal dialysis at home are present. But a gap in the market is found for the other blood purification treatments such as ultrafiltration, hemofiltration and especially for the hemodiafiltration.

In conclusion in Italy the absence, until now, of a marketed device able to perform HDF, HF and UF, was quite evident. The results found seem encouraging in filling the gap in the market for a machine that can also allow this type of home treatment. This way, the use of DIMI can lead to a decrease the total cost of dialysis in Italy, also reducing the costs of blood purification treatments considered and performed until now strictly in hospital. Future clinical studies are needed to define and confirm its optimal use, which may ultimately allow HHD to be considered in a bigger population of CKD patients.

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