Impact of different practice patterns on solute transport in peritoneal dialysis

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Abstract

Long term peritoneal dialysis (PD) is associated with increased peritoneal solute transport rate (PSTR) and loss of ultrafiltration capacity [1,2], both reflecting acquired structural alterations of the peritoneal membrane. Peritoneal functional changes correlate with hard outcomes, such as technique failure, increased risk of fluid overload and cardiovascular events [3,4]. Moreover, they correlate with encapsulating peritoneal sclerosis (EPS), a rare but severe complication of PD with nearly a 50% mortality rate [5,6].

Given the hard consequences of PSTR increase over time, understanding its determinants and developing clinical strategies to prevent or at least slow down this process might play a key role in PD patients' survival.

Over the last three decades, PD prescription strategies and clinical practice underwent some major changes, informed by both ongoing scientific evidence (growing awareness of glucose toxicity, association between fluid overload and hard outcomes) and manufacturing innovation (introduction of icodextrin, development of biocompatible dialysis solutions).

We performed a retrospective single-centre longitudinal analysis, from the early 1990s onward, and investigated the association of different clinical approaches with PSTR, and the association of PSTR with transfer to HD and patient survival.

The use of icodextrin and dry dwells was associated with long-term changes in membrane function, with icodextrin patients showing above average PSTR values, but a relatively flatter increase over time, and dry dwells on the other hand being associated with below average PSTR values, despite a relatively steeper increase over time.

PSTR was associated with both patient death and transfer to HD. The association between PSTR and outcome changed across time and it was affected by different clinical practice patterns.

We also analysed the determinants of PSTR at PD start, firstly conducting a single centre analysis, and subsequently validating our findings through a secondary analysis of the international multicentre Global Fluid Study.

We found evidence that PSTR at PD start changed in Stoke and across the UK over time. Different PD prescriptions can partly explain these changes, which seem to be linked to intraperitoneal inflammation, but further investigation is needed to clarify this phenomenon.

1. Introduction

1.1 Epidemiology of end stage renal disease and renal replacement therapies

End stage renal disease (ESRD) is a worldwide increasing phenomenon, representing a significant cause of both death and disability. The Global Burden of Disease study estimated that in 2015 1.2 million people around the world died from kidney failure (an increase of 32% since 2005). Moreover, 19 million disability-adjusted life years (DALYs) were directly attributable to reduced kidney function [7,8].

ESRD is a life-threatening condition, therefore affected people require a form of renal replacement therapy (RRT) to survive, be it a kidney transplant, haemodialysis treatment (HD) or peritoneal dialysis (PD). Across Europe, more than 600,000 people are on RRT, and nearly 90,000 new patients start treatment every year. Overall survival two years after starting RRT is 78%, varying between 75.6% on dialysis and 96.8% on transplant [9]. Despite improvement in the treatment of ESRD and its complications, life expectancy for people on RRT remains significantly shorter compared to the general population, as shown in figure 1 (adapted from [9]).

In the UK, according to the most recent renal registry report, 64,887 people were on treatment for ESRD in 2017 (+ 3.0% from 2016). Among them, more than 55% had a functioning kidney transplant, while the remaining were on dialysis (39% on HD, 5% on PD). In the same year, 8,001 new patients started RRT (+ 2.6% from 2016) and 90 days after starting treatment, 65% were on HD, 19% on PD and nearly 10% had a functioning transplant, while nearly 6% had died or interrupted the treatment [10].

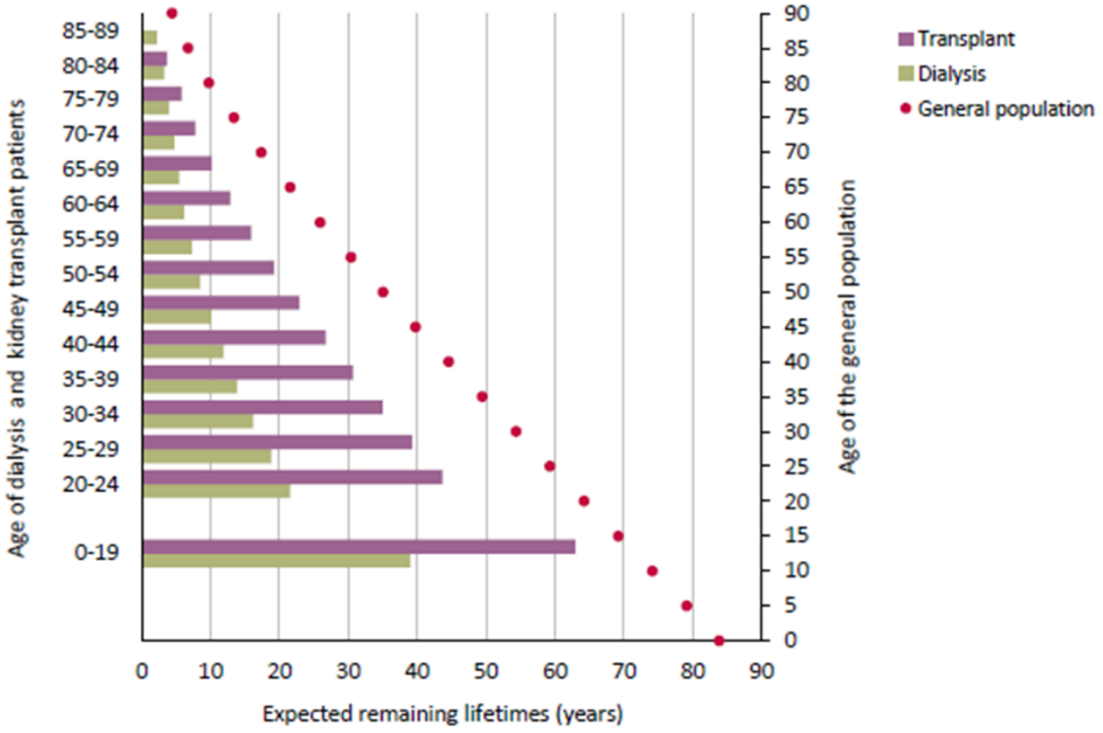


Figure 1: Expected lifetime for RRT patients compared to the general population, adapted from [9]

Data refer to a general population of 694 million people, from 37 countries within Europe or bordering the Mediterranean Sea.
Bars represent average expected remaining lifetime years for prevalent RRT patients, grouped by age. HD and PD data are combined. Dots mark the average expected remaining lifetime years for the general population, grouped by age.

1.2 Peritoneal dialysis (PD)

1.2.1 Basic concepts

PD is an alternative treatment modality to HD. Initially attempted in the 1940s as treatment for acute kidney injury, it became available as a routine treatment for chronic kidney failure only from the late 1970s. PD is a continuous treatment administered on a daily basis, rather than intermittently like HD. Moreover, it is a home rather than hospital-based treatment (even if home HD is also available). Finally, PD does not use an extracorporeal circuit and a plastic filter as dialyzer, but both blood clearance and ultrafiltration happen within the patient's body, in the abdominal cavity, through the peritoneal membrane.

The peritoneal membrane is a thin lining that naturally covers the inner surface of the abdominal wall and the majority of visceral organs. It consists of three main components: a layer of ciliated mesothelial cells, the underlying interstitial tissue, containing bundles of collagen and mucopolysaccharides, and a dense network of capillaries and lymphatics. It has a relatively large surface area (around 1 m^2), a high degree of capillarization (around 2 m^2 of capillary surface area per 1 m^2 peritoneal surface), and high blood flow (100–150 ml/min in adults) [11].

Under normal circumstances, the peritoneal membrane reduces the friction between visceral organs through the continuous production of small amounts of lubricants. During the PD process, instead, the membrane is challenged with litres of dialysis fluid and acts as a two-way semi permeable barrier, allowing solutes and water to cross from the bloodstream to the dialysate, but also permitting the absorption of different solutes from the dialysis fluid to the patient's bloodstream.

The capillary endothelium represents the functional barrier for transport of solutes and water, which happens mainly through a system of pores. Both in vivo studies and mathematical models tend to indicate the presence of three different types of pores: small pores (r 40-50 Å), large pores (radius approximately 250 Å), and ultrasmall pores (r 3-5 Å). Small pores are the most abundant and responsible for the transport of small molecules and ions; large pores, far fewer in number, allow transport of macromolecules (negligible under normal circumstances, but can increase significantly in response to inflammation); ultrasmall pores, recently identified with endothelial aquaporin–1, act as water selective channels (see figure 2 adapted from [11]).

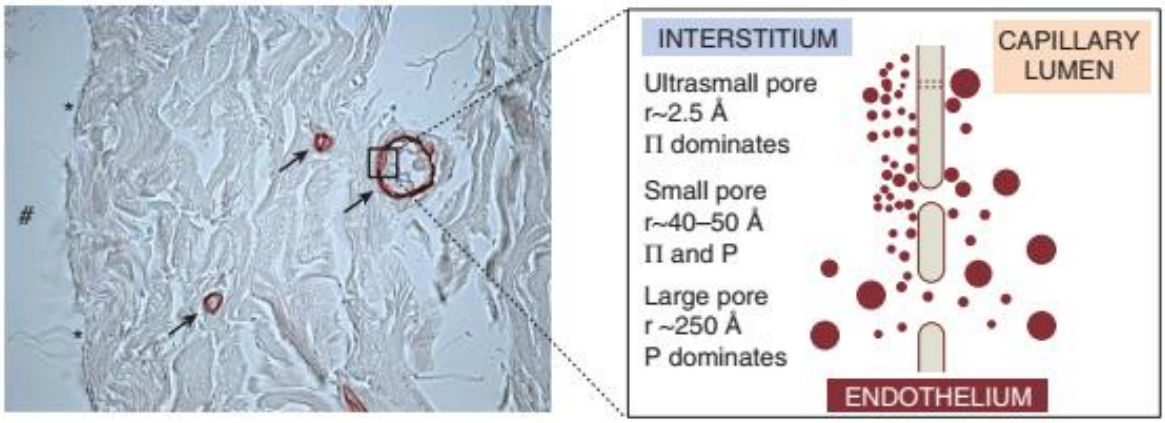


Figure 2: Peritoneal membrane structure and the three pore model, adapted from [11]

Left panel: peritoneal membrane cross section, stained for aquaporin -1.
 # peritoneal cavity
***** *mesothelial cell*
→ sub-mesothelial capillaries

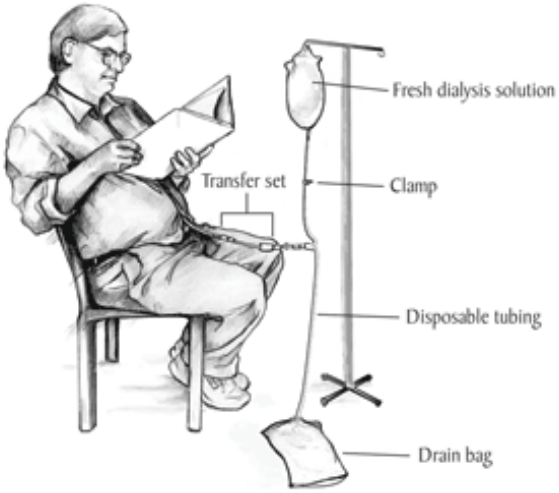
Right panel: three pore model
Starling forces operating across each type of pore are indicated, together with their size. (P, hydrostatic pressure; P, oncotic pressure)

Movement across the membrane happens thanks to a combination of diffusion and convection. Diffusion is the most important transport mechanism for low molecular weights solutes, like urea and creatinine. The driving force for diffusion through the small pore system is concentration gradient, that decreases during a dwell due to saturation of the dialysate, up to an equilibrium point where the diffusion net rate equals zero. Convection, on the other hand, accounts for the removal of solutes together with water and is driven by osmotic gradient. This is generated by the presence of glucose (or glucose polymers) in the dialysis fluid. Seeing as glucose can be absorbed during dialysis, both the osmotic gradient and the concentration gradient are dissipated during a dwell, and dialysis fluid needs to be periodically replaced in order to be effective. This is achieved using a permanent catheter dwelling inside the patient's abdomen. Through the catheter, dialysis fluid is periodically drained and replaced with fresh fluid, ensuring a continuous dialysis process by restoring the concentration gradient for solutes.

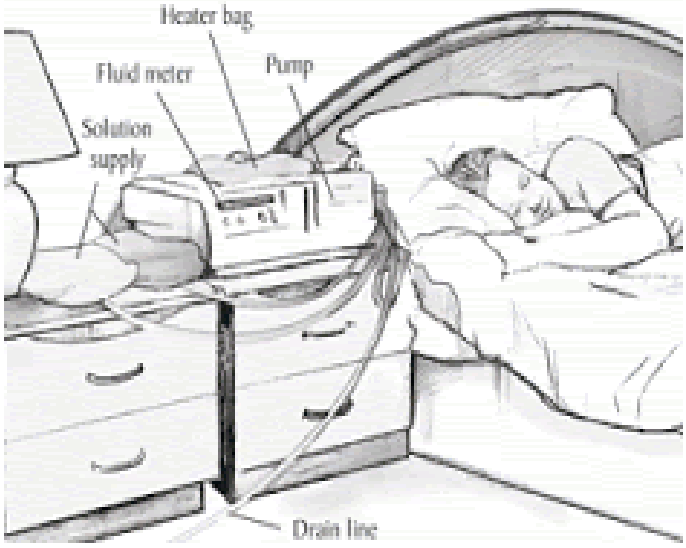
1.2.2 PD types: continuous ambulatory (CAPD) vs automated (APD)

As mentioned above, peritoneal dialysis is obtained by periodically introducing in the peritoneal cavity fresh dialysis fluid, that then is left to dwell in the abdomen for a set time before being drained out and replaced with new dialysis fluid.

The dialysate exchanges can be done manually (CAPD) or using an automatic cycler (APD).



CAPD was the first type of PD to be developed and to become available in the clinical practice, a reason for that being its extreme simplicity. It requires little equipment and the exchanges can happen in virtually any environment (granted it is kept clean and the patients can wash their hands). The dialysis kit, at its most basic, consists of a Y shaped connector with a clamp and two bags, one empty to drain the abdomen first, and a second one full of fresh dialysis fluid (typically 2 litres). Patients connect their catheter to the system and start draining the abdomen first. Subsequently, just moving the clamp from one arm of the connector to the other, they can close the draining bag that is now full of exhausted fluid, and open the fresh fluid bag instead, to fill the abdomen again. The driving force for all fluid movements is gravity, as shown in the cartoon. A typical CAPD regime consists of three exchanges during the day, and one longer dwell overnight. The fluid exchange itself takes roughly 30 minutes, and the subsequent dwell 4 to 6 hours during the day, and about 8 hours overnight. Alternative regimes may account for exchanges only during the daytime, and an empty abdomen overnight.



APD is in some respect an evolution of CAPD, using an automated cycler to perform the dialysis exchanges, typically at night. The first pioneering PD cyclers were designed in the 1960s, and only used to deliver in hospital intermittent PD (as opposed to HD). Starting from the 1980s cyclers underwent progressive improvement in terms of hardware and layout, making APD machines safer, quieter, less bulky and suitable for home treatment. It was only from the second half of the 1990s though that APD started to become widespread. The treatment requires an electricity powered cycler, but is fairly similar to CAPD in principle. Before going to sleep, patients connect their catheter to a Y shaped system, with the cycler to one end and an empty bag to the other. The cycler in turn is fed by bags of fresh fluid and it automatically switches between drain and fill mode at set times, alternating dwells and exchanges. APD allows for shorter dwells and more frequent exchanges, a feature that benefits particularly those patients that tend to absorb glucose quickly (as detailed in section 1.3.2). A typical regime includes 8h treatment overnight, exchanging around 10 litres of fluid, and a further long dwell during the day. Alternative regimes may account for exchanges only overnight, and an empty abdomen during the daytime.

1.2.3 PD fluids: standard, polymers, biocompatible

PD, similarly to HD, also works by means of a dialysis fluid, or dialysate. This is a solution with set pH and electrolyte concentrations, and variable concentrations of an osmotic agent to drive ultrafiltration (UF).

Standard dialysis fluids, the first developed and marketed, are glucose-based solutions containing variable concentrations of dextrose (D-glucose) as an osmolyte. Their pH is slightly acidic and they are buffered with lactate. Glucose effectiveness as an osmotic agent depends on the resistance the membrane can exert to its transport, described by the so-called osmotic reflection coefficient (σ). A σ value of 1 denotes the total reflection of a solute, whereas a σ value of 0 characterizes a fully permeable solute. With a σ of 0.03, glucose driven osmosis through the small pores is not particularly efficient, and yet accounts for 50% of the total ultrafiltration, as a consequence of the number and total surface area of small pores. On the other hand, osmosis through the ultrasmall pores is extremely efficient (because their diameter makes them impermeable to glucose, but allows free water transport) and it accounts for the remaining 50% of ultrafiltration, despite the much smaller total surface area. Through small pores glucose can cross the membrane in both directions, and can therefore be absorbed from the dialysate. Glucose absorption is around 60% of the instilled quantity by the end of a 4-hour dwell, and 75% after 6 hours [12]. Glucose concentration gradient is therefore maximal during the start of a dialysis exchange and decreases during the dwell, and so does the transcapillary UF rate.

PD fluids commercially available contain three basic glucose concentration, respectively 1.36% (also called 1.5%, when referring to glucose as monohydrate dextrose, rather than anhydrous), 2.27% (or 2.5%) and 3.86% (or 4.25%, also called hypertonic). By increasing

glucose concentration, UF rate also improves, but this comes at a price. Numerous studies in fact have shown that glucose exposure is associated with significant damage to the peritoneal membrane, as detailed in the following chapter [13,14]. On the other hand, adequate UF is vital for PD patients, especially when their residual renal function decreases, and if not achieved leads to systemic fluid overload, which is in turn associated with increased cardiovascular morbidity and mortality [3,4].

Finding the right balance to keep patients euvolemic whilst avoiding glucose toxicity represents a clinical challenge, and it called for researchers and manufacturers to try and develop alternative dialysis fluids. **Glucose polymer solutions** were developed in the 1990s to try and answer this call, and introduced on the market (under the name of icodextrin) as an alternative to hypertonic glucose solutions. Icodextrin is a polydispersed mixture of glucose polymers, with an average molecular weight of 16800 D. Due to its high molecular weight, it acts as a macromolecule and induces UF through colloid osmosis (independently from the PD fluid tonicity) through the small pore system. Unlike glucose, icodextrin is poorly absorbed during a dialysis dwell, thus generating a more stable UF rate that is sustained over time.

Since its introduction on the market, icodextrin has grown in popularity, and it has indeed changed PD practice quite dramatically. Offering a valid alternative to hypertonic glucose solutions, it has enabled patients with a poor residual kidney function and/or an elevated solute transport rate to manage their fluid balance effectively and potentially to remain on PD treatment for longer reducing the need to switch to HD. Two different meta-analyses showed its efficacy in preventing episodes of acute fluid overload, and there is moderate evidence that it may improve survival in PD patients [16,17].

Despite these advantages, icodextrin use is not completely harm-free. Soon after its introduction, in the early 2000s, several case reports documented the association between icodextrin and both diffuse skin rashes and acute sterile peritonitis, likely caused by hypersensitivity reactions [18]. It is not clear whether those cases represented a reaction to icodextrin itself, or rather to contaminants resulting from the manufacturing process. Bacterial derived peptidoglycan was investigated as a possible cause for the outbreak, and a positive relation between peptidoglycan concentrations in recalled dialysate and reports of aseptic peritonitis was detected. Even at concentrations considered safe according to the pharmacological standards of the time, peptidoglycan was able to induce a significant inflammatory response in human peripheral mononuclear cells, supporting the hypothesis that contaminants rather than icodextrin itself were responsible for the peritonitis [19]. This is possible since despite the increase in icodextrin use in more recent years, the number of reported adverse reactions decreased (possibly as a consequence of improved manufacturing).

Last arrived on the market, **biocompatible fluids** are another example of alternative PD solutions specifically developed to try to reduce dialysis induced toxicity to the peritoneal membrane. PD fluid toxicity is thought to originate from a combination of low pH and high content in glucose degradation products (GDPs). GDPs are by-products of the standard fluid manufacturing, that originate during the high temperature sterilization of the fluid itself, which causes a "caramelisation" of dextrose. They are characterised by in vitro cellular toxicity, mainly affecting mesothelial cells [20,21]. They can also induce TGF-β and VEGF, which in turn cause fibrosis and vascular proliferation of the sub-mesothelial layer [22,23]. Moreover, besides their direct toxicity, GDPs promote formation of advanced glycation end products (AGEs), causing a range of damage similar to what can be observed in uncontrolled diabetes.

Biocompatible fluids are glucose-based PD solutions characterised by a lower content of GDPs, when compared to standard ones. Moreover, they are pH neutral and buffered with bicarbonate or a mixture of bicarbonate and lactate rather than lactate alone. Their lower GDPs content is achieved thanks to a different manufacturing process, whereby the fluid comes split into a two-chamber bag, keeping the acidic and alkaline components separate during the whole sterilisation process and up until the patient is ready to use the fluid. This allows for glucose to be sterilised in the acidic compartment at a very low pH, thus reducing the formation of GDPs. The two-chamber bags are then mixed by the patients themselves just before use, just breaking a frangible pin that keeps them separate.

Despite the theoretical advantages offered by a reduction in GDPs, and biopsies showing beneficial effect on the peritoneal membrane [24, figure 3], strong evidence in favour of a significant clinical impact of biocompatible fluids is still missing. There is some consistency in associating biocompatible fluids and better preservation of residual kidney function, as highlighted by a recent meta-analysis [25]. There is no clear evidence, however, whether biocompatible fluids can preserve the peritoneal membrane function over time and protect against peritonitis damage [26-28]. Nevertheless, based on in vitro evidence and histopathological findings, there is a general trend towards biocompatible use in the clinical practice, and this will enable further clinical trials to try and prove their efficacy.

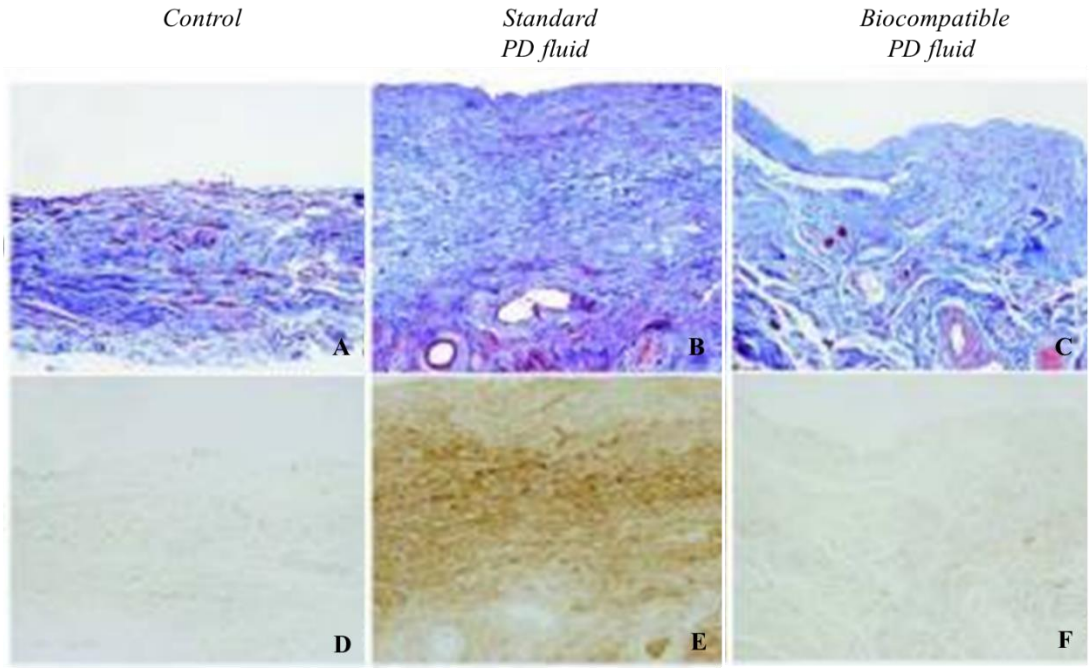


Figure 3: Impact of biocompatible fluids on the peritoneal membrane structure, adapted from [24]

Peritoneal membrane cross sections, 20x original magnification. Panels A-C: Masson trichrome staining. Panels D-F: immunostaining for AGEs. Standard fluids are associated with increased fibrosis in the submesothelial compact zone and hyalinazin degeneration of collagen fibres (B), as compared to pre-PD peritoneal biopsies (A) and biocompatible fluids (C). AGEs deposition is also more preminent (E, as opposed to D and F).

1.2.4 PD impact on the peritoneal membrane

By all means, PD represents an "improper use" of the peritoneal membrane and a significant stress to its physiology. PD treatment exposes patients to the risk of both acute and chronic intraperitoneal inflammation, both associated with major anatomical and functional changes to the membrane.

Acute inflammation is predominantly secondary to infective peritonitis, one of the main complications of PD treatment (unsurprisingly, seeing as glucose-based dialysate represents an ideal medium for bacterial growth and the PD catheter offers a port of entry to the peritoneal space). Inflammation can also result from chemical or "sterile" peritonitis, an acute hypersensitivity reaction to the dialysis fluid itself, as previously mentioned about

icodextrin. Irrespective of the cause, acute inflammation is characterised by nitric oxide mediated vasodilation and increase in the peritoneal capillary blood flow [29]. These haemodynamic alterations can be seen as an enlargement of the vascular surface area that is available for solute transport. Functionally, they are therefore associated with an acute increase in peritoneal solute transfer rate (PSTR). These acute changes are transient and reversible once the peritonitis has resolved, although there is some evidence that repeated episodes of acute inflammation (like clusters of peritonitis) can result in some degree of persistent damage to the membrane [30].

Chronic subclinical peritoneal inflammation, instead, has been widely investigated in more recent years as a possible driver for the permanent anatomical and functional alterations to the peritoneal membrane observed in long term PD patients. Prolonged exposure to non-physiologic dialysis solutions is associated with anatomic alterations that affect mainly the sub-mesothelial layer, characterised by vascular proliferation, vasculopathy and fibrosis [31,32]. A subgroup of patients ultimately develops encapsulating peritoneal sclerosis (EPS), the most severe form of peritoneal fibrosis, leading to bowel encapsulation and obstruction, malnutrition, and a high risk of death [5,6] (see figure 4, adapted from [6]).

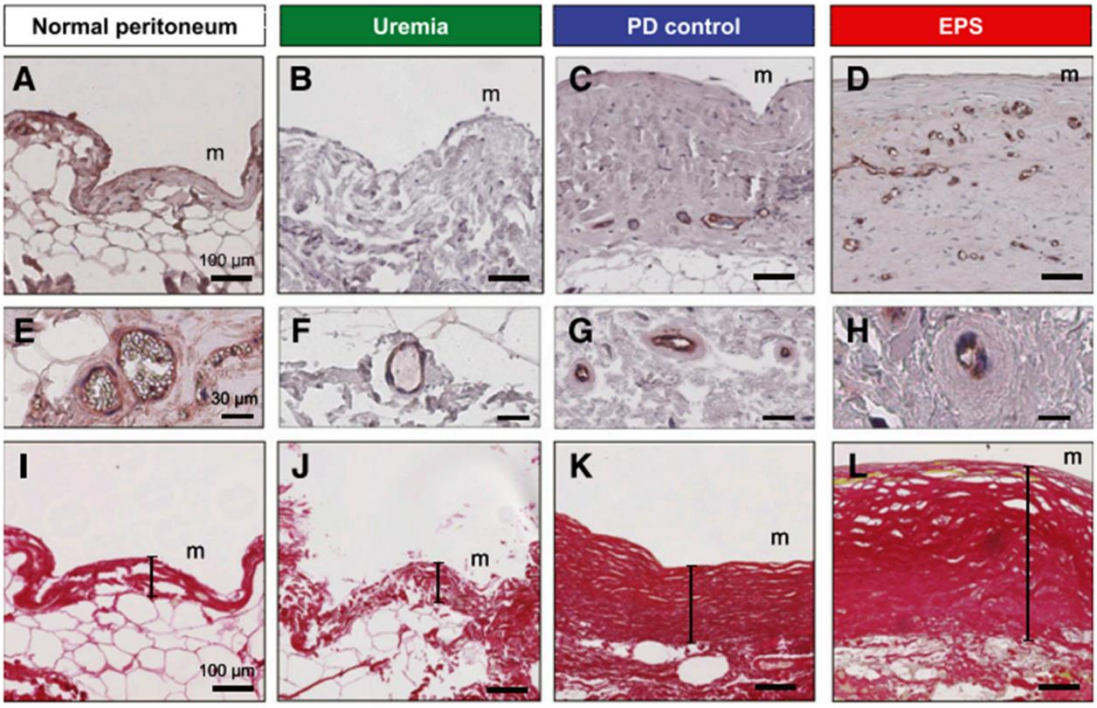


Figure 4: Changes to the peritoneal membrane anatomy associated with ESRD and impact of long- term PD and EPS, adapted from [6]

The peritoneal membrane anatomy changes in response to uremia, PD treatment and during EPS. Changes are most evident in both the vascular and submesothelial structure.
A-H: Peritoneal membrane cross sections. Immunostaining for vonWillebrand factor showing progressive vascular proliferation (A to D, 20x original magnification) and increase in vascular thickness (E to H, 40x original magnification) in normal, uremic, PD and EPS patients.
I-L: Peritoneal membrane cross sections. Representative sections of parietal peritoneum stained with picrosirius red, showing progressive increase in submesothelial thickness (black bar) in normal, uremic, PD and EPS patients.

Functionally, long term PD patients experience a progressive rise in peritoneal solute transport rate, with consequent faster absorption of glucose and dissipation of the osmotic gradient, which is in turn associated with a reduction in the ultrafiltration capacity [1]. Rise in PSTR and fall in UF are not just two sides of a same coin, though. Davies et al [1] showed evidence of a possible mismatch in trend between the two which becomes more marked after 4 years of treatment, although in the study there is more variability in UF measures in this period (see figure 5, adapted from [1]).

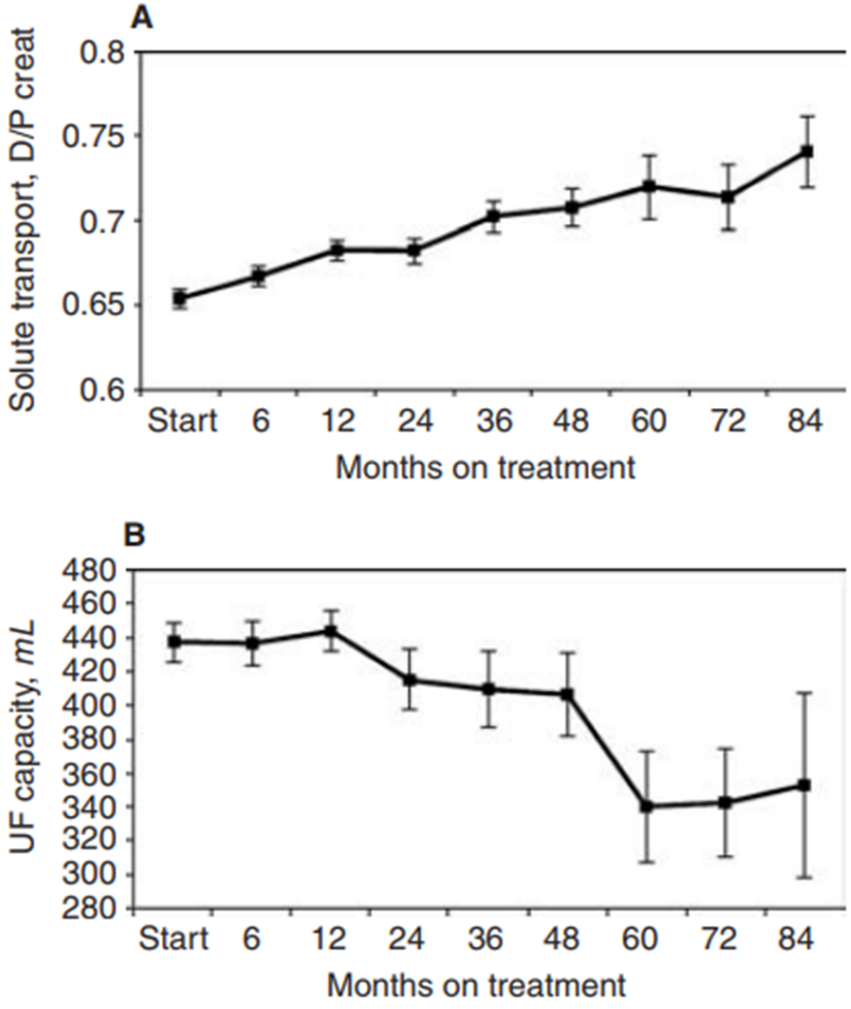


Figure 5: Long term changes in solute and water transport, adapted from [1]

Data are expressed as mean and standard deviations. During follow up, progressive rise in PSTR (A) is associated with decrease in UF capacity (B). The drop in UF after 48 months on treatment, though, appears disproportionate to the increase in PSTR, suggesting other mechanisms are likely involved and the reduction in UF capacity is not a mere consequence of increased solute transport through the small pores. This initial observation has been validated in more recent studies, and attributed to increased sub-mesothelial fibrosis, interfering with the ultrasmall pores free water transport.

This original observation has been in more recent years attributed to a progressive reduction in the hydraulic conductivity of the peritoneal membrane, which is in turn attributed to sub-mesothelial fibrosis becoming prominent in long term PD patients [33]. Sub-mesothelial fibrosis interferes with water flow via both small and ultrasmall pores. Impaired water transport across the ultrasmall pores can be also manifested by a reduction in sodium sieving

(the early dilution of dialysate sodium observed during a dialysis dwell, secondary to free water transport from the bloodstream to the abdominal cavity through the aquaporins).

Interestingly, numerous studies have now shown a strong association between the rise in PSTR and intraperitoneal production of inflammatory cytokines, especially interleukin 6 (IL-6), supporting the hypothesis that long-term changes in membrane function and chronic inflammation may be linked [34,35]. Experimental studies can help understanding this association, seeing as IL-6 has been linked with both peritoneal angiogenesis and fibrosis, both known to impact PSTR. With regards to angiogenesis, intraperitoneal IL-6 is involved in the expression of Vascular Endothelial Growth Factor (VEGF) by human mesothelial cells. In a mouse model, induction of peritoneal inflammation in wild type and IL-6 deficient mice results in significantly different expression of VEGF and new vessels formation [36]. With regards to fibrosis, in vivo studies where peritoneal membrane fibrosis is triggered by repeated inflammatory episodes (somehow mimicking what could happen with recurrent peritonitis), IL-6 knockout mice don't develop peritoneal fibrosis in response to inflammation. In the same model though, overexpression of IL-6 is not associated with worse fibrosis, thus suggesting that the cytokine is necessary to develop a fibrotic response, but is not directly causing it [37].

Further studies are needed to validate these findings and to get a better understanding of the molecular pathways responsible for the structural and functional changes that the peritoneal membrane undergoes with time on PD. Specific cytokines may in fact represent a molecular target for treatment of peritoneal inflammation and fibrosis, with important consequences for PD patients.

As previously mentioned, in fact, long term changes to the peritoneal membrane and specifically loss of ultrafiltration capacity can significantly affect patients' life. First of all,

reduced ultrafiltration calls for the patients to restrict their fluid intake in order to avoid the risk of acute fluid overload and pulmonary oedema, with consequences on their quality of life. Secondly, the inability to manage fluid balance effectively limits long-term use of PD treatment and is one of the reasons to transfer to HD, which again has a significant impact on patients' independence and quality of life. Finally, loss of UF affects long term survival, as chronic water and sodium retention are associated with adverse cardiovascular events and increase mortality [3,4].

1.3 Peritoneal equilibration test (PET)

1.3.1 Basic concepts

Unlike HD, where the dialyzer is a synthetic filter with standard specifications set by the manufacturer, PD relies on a biological membrane, with unique characteristics which differ between patients. As such, the dialytic performance of an individual's peritoneal membrane is not standard, and cannot be predicted based on the patient's biometrics or demographics, but needs to be assessed individually after the onset of PD. Moreover, as previously mentioned, the dialytic performance can change over time, as a consequence of the membrane's vintage and anatomic alterations, and needs to be monitored.

Seeing as the main goals of any dialysis treatment are the removal of uremic toxins and excess water, together with the correction of pH and electrolytes imbalances, the main variables of interest when assessing a membrane are its permeability to solutes (peritoneal solute transport rate, PSTR) and ultrafiltration capacity (UF).

The rate at which a solute can transfer across the membrane is described by its diffusion capacity, or mass transfer area coefficient (MTAC). This is the theoretical maximal rate of clearance by diffusion for a given solute, which occurs when its concentration is zero in the dialysate. In the clinical setting, MTAC is estimated using the solute dialysate-to-plasma concentration ratio. This is clearly an approximation of the true MTAC, but it is widely accepted (for its simplicity) and considered reliable for solutes where the diffusion capacity is much greater than the UF rate.

A common and easy way to test the membrane is the peritoneal equilibration test (PET), originally described by Twardowsky in 1987 [38]. This is a semiquantitative assessment, based on the assumption that solutes have different concentrations between the peritoneal

capillary blood and the dialysate, but will eventually reach an equilibrium. The rate of their equilibration depends on the "permeability" of the membrane, therefore given a standard amount of dialysis fluid (with known solutes composition) and a set time, the difference in concentration found between dialysate and plasma for a specific solute (D/P ratio) reflects the amount of solute that has been transported through the membrane, that is the PSTR. This ratio can theoretically be determined for any solute, but in clinical practice only creatinine is routinely tested, as a marker of small molecule transport (D/P Cr). The higher the D/P Cr (closer to one), the faster the solute transport across the membrane. Creatinine is an easily measured byproduct of muscle metabolism, produced by the organism at a fairly stable rate and excreted unmodified by the kidneys. Nephrologists are familiar with it, as creatinine clearance is routinely used to estimate glomerular filtration rate. In PD patients, creatinine is used both to measure PSTR and peritoneal clearance (which can be added to the residual renal clearance and provides a simple marker of peritoneal dialysis adequacy).

PET can also be used to assess the transport of glucose. Unlike creatinine, once absorbed from the abdominal cavity glucose is quickly metabolized and thus removed from the bloodstream. In this scenario, a conventional D/P ratio would be meaningless. The fraction of glucose absorbed, instead, can be determined comparing the dialysate glucose concentration at a specific time (t) to the initial concentration (Dt/D0). The higher the Dt/D0 (closer to one), the slower the glucose absorption.

Finally, PET is useful to determine the membrane permeability to water, or UF capacity. This is calculated as the difference between the volume infused at the beginning and the volume drained at the end of a standard PET. A volume of UF less than 100 ml is diagnostic of ultrafiltration failure (UFF) when using 2.27% glucose (less than 400 ml when using 3.86%).

The test originally described by Twardowsky, or “standard PET”, is performed using 2 litres of 2.27% glucose and the duration of the dwell is set to 4 hours. Alternatively, PET can be performed using 3.86% glucose, to better assess free water transport and sodium sieving. Based on the same principles as the original PET, further tests have been developed in more recent years (mini-PET, double mini-PET), allowing for a refined characterisation of solute and water transport. For a detailed description of these tests refer to La Milia [39]. Standard PET remains a useful tool though for a simple “first line” assessment of the membrane.

The main advantages of PET are in fact its simplicity and reproducibility. By standardizing a few crucial steps (volume infused, glucose concentration, infusion and dwell length) it is possible to use PET results not only to compare results between patients (within a centre or between populations) but also to monitor a single patient performance over time, adjusting the dialytic treatment accordingly, as detailed in the following section.

1.3.2 PET results in clinical practice

Testing the peritoneal membrane has important consequences in clinical practice, and is therefore recommended as a routine practice at PD start, and subsequently at least every 12 months, or more frequently if clinically indicated [40]. Knowing the membrane characteristics can in fact inform PD prescription, enabling the clinician to tailor and optimise the dialysis treatment, and also help in the differential diagnosis of PD complications [41].

Based on the results from a traditional PET with 2.27%, PD patients can fall into 4 different classes of transporters: high (H), high average (H/A), low average (L/A), low (L). The classification dates back to the original work from Twardowski, and the upper and lower limit of each class refer to the mean and standard deviation of a specific population. The

terms “high” and “low” have been subsequently questioned, as they seem to indicate a high transporter can achieve a better clearance than a low one. This is not necessarily true, and patients would be better described as fast, average or slow transporters instead, to reflect the membrane actual behaviour during PD. A fast transporter, in fact, does not clear more creatinine than a slow transporter. On the contrary, due to the early equilibration between plasma and dialysate, the diffusive gradient will be reduced and the amount of creatinine removed depend only on convective transport, therefore on the UF achieved at the end of a dwell. Effectively, a fast transporter will likely remove less creatinine than a slow transporter during a 4 hours dwell on CAPD, and would perform much better with short dwells on APD.

Individual transport characteristics must guide the clinician when prescribing PD treatment, as summarised in table 1 (adapted from [40]). It is also important to remember that membrane function can change significantly over time, therefore needs to be periodically monitored to adjust treatment accordingly.

Table 1. Peritoneal membrane transport classes and their clinical management

Transport class	**Properties**	**Recommendations**
Fast	Fast equilibration of creatinine, Typically, D/P Cr >0.80 after 4 h Fast dissipation of glucose from the peritoneal cavity, negative UF in dwells with 1.36% > 180 min	Short dwells (preferably <180 min). Icodextrin to be considered for long dwell, unless sufficient residual diuresis
Average	Moderate equilibration of creatinine, steeper slope in the beginning of the dwell Negative UF only >240 min	Avoid dwells <120 or >300 min, except for one daily “long dwell”
Slow	Slow equilibration of creatinine, Typically, D/P Cr <0.55–0.60 after 4 h Sustained UF even in dwells > 240 min	Long dwells, preferably >240 min Use larger volumes rather than more dwells

Table 1. Peritoneal membrane transport classes and their clinical management, adapted from [40]

PET results can not only inform PD prescription, but also help with the differential diagnosis of common PD complications. The test is particularly useful in case of patient overhydration, as it can differentiate between a true membrane deficit in water transport and other common problems, like catheter related mechanical outflow problems or patient related poor compliance to fluid restriction [42].

1.3.3 PET results and hard outcomes prediction

Peritoneal membrane function is not only important to inform PD prescription, but also as a risk factor of patient mortality. As previously mentioned, high solute transport and low ultrafiltration capacity are associated with worse outcomes, such as increased cardiovascular morbidity and mortality [4,43].

The association between high PSTR and mortality was initially observed in the late 1990s, and was considered counterintuitive seeing as dialysis clearance of small solutes was thought to be a marker of optimal dialysis efficacy [3,44,45].

It was assumed that the rise in PSTR could represent a marker of systemic inflammation, or endothelial dysfunction, and as such increase the risk of mortality. More recent studies seem to have proven this assumption wrong, as local intraperitoneal inflammation and systemic inflammation must be considered separate entities. Nevertheless, increased PSTR is associated with intraperitoneal inflammation and may result in a backflow of inflammatory cytokines to the bloodstream, with still unknown systemic effects [35].

Other studies seem to indicate that the link between increased PSTR and mortality could be chronic fluid and sodium retention. The association with increased mortality is in fact particularly strong in CAPD, but not in APD (that, as previously mentioned, allows fast transporter to manage their fluid balance more effectively) [4]. Moreover, the association

seem to lose its strength once a patient has transferred to HD, suggesting no direct cause-effect relationship between transport status and mortality [45]. In this study, though, only PSTR at PD start was tested, and this may not be the best approach as PSTR changes over time (and last measured PSTR before switching to HD might have been more informative).

Another possible link between increased PSTR and mortality may be represented by increased protein loss through the peritoneal membrane. PSTR is associated with protein loss primarily through the mechanism of local inflammation [46]. This might contribute to chronic fluid retention, reducing plasma oncotic pressure, but there is still significant uncertainty in the interpretation and value of peritoneal protein clearance.

1.4 **Hypotheses**

Given the significant clinical impact of PSTR increase over time, understanding its determinants and developing clinical strategies to modify its natural time course might play a key role in PD patients' survival.

We hypothesised that different PD regimes that became available from 1990 (characterised for example by different PD fluid glucose concentrations, the use of icodextrin, the use of biocompatible solutions or the option of a dry long dwell) may have affected the time course of PSTR observed during follow-up.

We also observed differences in PSTR at PD start (within 3 months after initiation of PD treatment) between incident cohorts of PD patients across calendar years, and we hypothesised that different PD regimes may be associated with early changes in PSTR possibly via intraperitoneal inflammation.

We hypothesised that PSTR may be associated with patient survival and transfer to HD. We hypothesised that the association between PSTR and outcome changed across time and may be affected by difference clinical strategies and PD regimes.

2. Patients and methods

2.1 Population

Three different cohorts were included in the research project, and analysed separately to test our hypotheses, as detailed below.

The Stoke cohort was used to investigate the effect of different PD regimes on PSTR time course. This is a large, single centre cohort of PD patients from the United Kingdom, very well characterised in terms of demographics, comorbidities and PD treatment features. Clinical data were collected consistently, at regular intervals for each patient during follow-up, covering a time frame of nearly 30 years from 1990 to 2016 without interruptions. It therefore allowed for the analysis of both longitudinal changes in PSTR as well as differences in PSTR at PD start observed across patients starting PD in different calendar years.

The Global Fluid cohort was used to replicate the analysis of changes in PSTR at PD start observed in Stoke. This is a large, multicentric cohort including PD patients from the United Kingdom, Korea, and Canada. It is very well characterised in terms of demographics, comorbidities and PD treatment features. It also includes measurements of biomarkers of peritoneal inflammation, such as IL-6, and therefore allowed for inflammation to be investigated as a possible determinant of early changes in PSTR. It covers a shorter time frame, from 2002 to 2008.

Cardiff and Swansea cohorts were used to further replicate the analysis of changes in PSTR at PD start observed in Stoke, looking at changes happening in the early 90s (a time frame not covered by Global Fluid). These cohorts were poorly characterised in terms of demographics, comorbidities and PD treatment features (as they mainly included PET

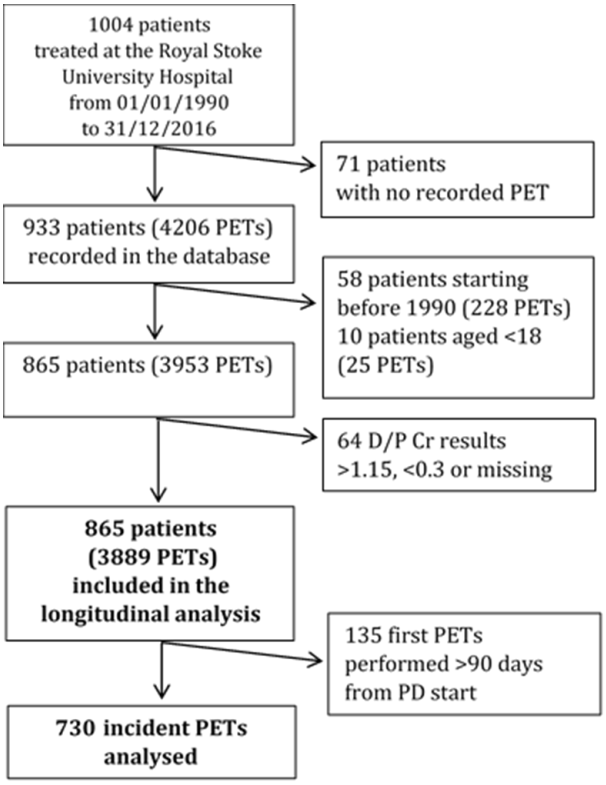
measurements) but they offered the advantage of a relatively consistent collection of data on PSTR from 1995 to 2019.

With regards to ethical approval, data from the Global Fluid dataset were previously published and full details on the ethical approval can be found in the original paper [35]. For the analysis of Stoke, Cardiff and Swansea datasets, we followed guidance provided by the National Research Ethics Service. The analysis was aimed at evaluating current care against outcomes, and as such did not require Research Ethics Committee review. No intervention nor randomisation were applied. Data from all datasets were fully anonymised and shared across centres for the purpose of service evaluation.

2.1.1 Stoke cohort

All incident PD patients aged >18, starting PD at the Royal Stoke University Hospital from 01/01/1990 to 31/12/2016 and having at least 1 PET recorded during their follow-up were included in the cohort. Follow-up time ranged from 9 days to 12.8 years (median 2 years).

Clinical data (demographics, comorbidities, data on PD regime and fluids, PET results, patients and technique outcome) were collected using the local database. 3889 PETs from 865 patients were included in the longitudinal analysis of PSTR changes. 730 PETs from 730 patients were included in the analysis of determinants of PSTR at PD start (see flowchart 1).



Flowchart 1: Stoke Cohort features

2.1.2 Global Fluid cohort

All incident PD patients aged >18 included in the Global Fluid Study, having a PET recorded within the first 90 days from PD start were included in the cohort.

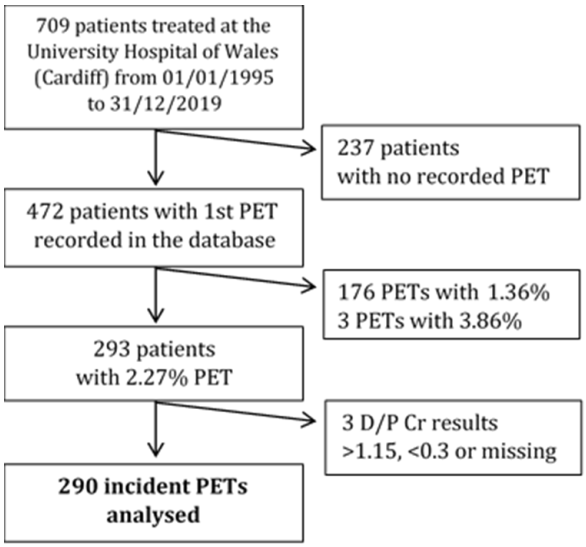
The Global Fluid Study was an international, multicentre study including adult PD patients treated at ten different centres from the United Kingdom, Korea, and Canada.

It recruited patients from 2002 to 2008, and clinical data were collected and stored in a purpose-built database. For a detailed description of the Global Fluid study, see Lambie et al. [32]. A total of 566 incident PETs were included in the analysis of determinants of PSTR at PD start.

2.1.3 Cardiff cohort and Swansea cohort

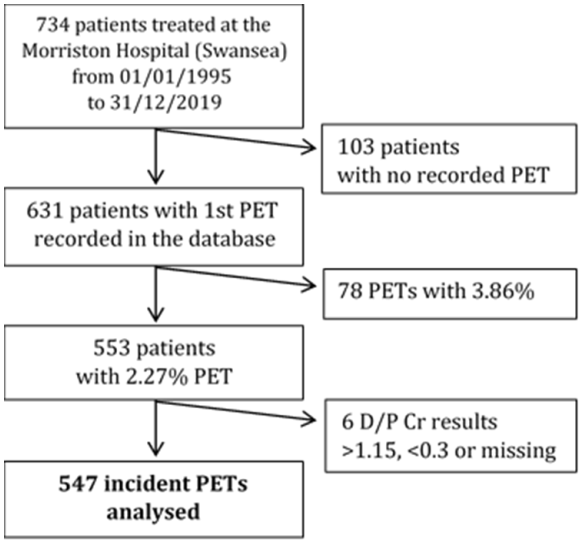
All patients aged >18 treated with PD at the University Hospital of Wales (Cardiff and Vale University Health Board) from 01/01/1995 to 31/12/2019 were included in the Cardiff cohort.

Clinical data were collected using the local membrane transport database, originally including 709 patients. 290 patients were included in the final analysis, accounting for 290 PETs (see flowchart 2).



Flowchart 2: Cardiff Cohort features

All patients aged >18 treated with PD at the Morriston Hospital (Swansea Bay University Health Board) from 30/06/1995 to 31/12/2019 were included in the Swansea cohort. Clinical data were collected using the local membrane transport database, originally including 734 patients. 631 patients were included in the final analysis, accounting for 631 PETs (see flowchart 3).



Flowchart 2: Swansea Cohort features

2.2 Methods

As regards the Stoke cohort, demographic characteristics and comorbidities were recorded at PD start. Comorbidities were documented using the validated Stoke Comorbidity Index [47].

Biometrics, blood results and PD-related measurements were recorded at each PET measurement occasion, and assumed to be constant in between PETs. Number of peritonitis was recorded at each PET measurement and refers to the number of episodes prior to the PET.

As regards PD-related measurements, practice patterns such as type of PD prescribed (CAPD or APD), use of icodextrin, use of biocompatible solutions and use of a dry dwell were recorded as binary variables. Residual renal function (RRF, expressed as residual urine volume), daily ultrafiltration, number of peritonitis episodes and estimate of glucose exposure were recorded as continuous variables.

PET was performed in all patients at PD start (within 90 days from the beginning of treatment) and then routinely every 6 months, as part of clinical follow-up.

PSTR was expressed as dialysate to plasma creatinine ratio (D/P Cr) after a 4-hour standard PET with 2.27% glucose concentration. Even if glucose concentration does not significantly affect PSTR [48], alternative PETs performed with 1.36% or 3.86% glucose (in Cardiff and occasionally Swansea cohort) were discarded from the final analysis for consistency. Only D/P Cr results between 1.15 and 0.3 were considered reliable and therefore included in the analyses, in line with previously published studies [49].

In measuring UF, dialysate bag overfill was accounted for [50] and an average correction factor of 200ml was subtracted from the effluent volume, thus accounting for the line flush. Appropriate correction was also applied when estimating daily UF in CAPD patients.

Correction was not applied to APD patients, where the cycler manages the line priming and subsequent volume of infused dialysate.

Peritoneal glucose exposure is not univocally defined in the literature, and different estimates have been used to assess it. In this study we derived peritoneal glucose exposure from the PD prescription menu, defining it as the average concentration of glucose prescribed on a daily basis. Icodextrin and amino acids exchanges were excluded from the calculation of volumes. In a typical CAPD regime, made of 4 dwells with 2 litres of fluid each, a patient receiving two 1.36% bags, one 2.27% bag and one icodextrin bag overnight would have the following glucose exposure estimate [(1.36*4000) + (2.27* 2000)]/6000= 1.66. By calculating glucose exposure like this, we focused more on the potential effect of glucose peak concentration, rather than the cumulative daily amount.

Different laboratory techniques were used over time to measure serum and dialysate creatinine in the Stoke cohort, and the difference in their accuracy had the potential to introduce a significant bias in the statistical analysis. In particular, creatinine was estimated with Jaffe colorimetric assay until 28/10/2008. It is known that this test is subject to glucose interference, therefore appropriate correction for the dialysate glucose concentration was applied to estimate dialysate creatinine concentration, as part of routine clinical practice. Subsequently, the laboratory switched to ELISA enzymatic assay, more accurate and not affected by glucose. The different accuracy between the two assays has been estimated in our data and resulted in a 4% average difference in the D/P creatinine after the laboratory switch, which has been accounted for and corrected in the statistical analysis.

Plasma albumin also resented from a change in laboratory assays in Stoke, being measured with bromocresol green before 2007 and bromocresol purple afterwards. We therefore adopted a validated conversion factor to compare the results [51].

As regards the Global Fluid cohort, please refer to Lambie et al. [35, table A1 in appendix].

As regards the Cardiff and Swansea cohorts, only minimal demographic information was available alongside membrane transport data. No information on comorbidities, body measurements and PD prescription were recorded. The first PET measurement recorded for each patient in the database was assumed to represent their membrane function at PD start.

2.3 Statistical analysis

Continuous variables are described using mean and standard deviation or median and interquartile range, categorical data are described using frequencies and percentages.

The impact of different PD regimes on the natural course of PSTR over time was analysed using the Stoke cohort via linear mixed-effects model accounting for clustered data (multiple PETs per patient). PD related variables of clinical interest (such as the use of icodextrin, biocompatible solutions or dry dwells) were selected a priori. Explanatory variables known to affect PSTR from previously published literature (such as demographics, comorbidities, residual renal function and peritonitis episodes) were also included in the model where there was consistent evidence of an association [30,43,44]. Other variables of uncertain relevance (such as BMI or the use of APD vs CAPD) were tested for an association in a multivariable model and excluded if there was no clear association with PSTR (adopting a p value threshold ≤ 0.2).

Time was included in the model both as continuous linear variable, representing years of follow-up from PD treatment initiation, and as a categorical variable indicating the calendar year of PD start. Interaction of covariates with follow-up time was also included in the model. Linearity of time varying variables (such as number of peritonitis episodes or residual urine volume) was checked with scatter plots.

Sensitivity analysis was carried out refitting the model excluding PETs performed in the first 6 months of follow-up (where data variability is higher as a consequence of a more instable clinical behaviour of the peritoneal membrane).

Determinants of PSTR at PD start were analysed using the Stoke cohort via multivariable linear regression. Both patient-related covariates (gender, BMI, diabetes, residual renal function) and treatment related explanatory variables (average glucose concentration, use of icodextrin, biocompatible solutions, dry long dwell, timing of PET) were included in the model. Initial results were replicated using the multi centric Global Fluid cohort, fitting a secondary analysis of the Global Fluid study including only incident patients and PETs performed within the first 90 days from PD start. Variable selection for the multivariate regression was performed in a similar way to the linear mixed-effects model.

The impact of PSTR on patients and technique survival was assessed using the Stoke cohort via Cox proportional hazards regression for cause-specific hazards. PSTR was included in the model as time varying variable. A further model was fitted including PSTR at baseline (time invariant) and PSTR interaction with calendar time, to assess whether the impact of PSTR on outcome changed across incident cohorts. A third model was fitted including PSTR at baseline (time invariant) and PSTR increase from baseline (time varying) to specifically assess the impact on outcome of PSTR rate of increase over time rather than absolute value.

In mixed-effects linear regression models, non-parametric LOWESS (Locally Weighted Scatterplot Smoothing) was used for graphical display.

As part of the regression models diagnostics, distribution of residuals was tested using quantile-quantile plots. Heteroscedasticity was checked plotting residuals against fitted values. Collinearity was checked calculating the variance inflation factor for the model. In the linear mixed-effect model diagnostic, both a linear random intercept and a linear random

intercept and slope model were fitted. A likelihood ratio test was used to compare the two, showing a better fit for the random intercept and slope model.

As part of the survival analysis diagnostics, Shoenfeld residuals were used to check the proportional hazards assumption.

The statistical analysis was performed using Stata.15.

3. Results

3.1 Analysis of the Stoke cohort

Within the Stoke cohort, both patients' characteristics and clinical practice patterns changed significantly over the last three decades, as summarized in table 2.

3.1.1 Changes in PD population

Across time, the main differences in PD population were related to age, diabetes, BMI and residual renal function. From 1990 onwards, the average age of incident PD patients increased, together with the proportion of diabetes, average BMI and residual urine volume.

The proportion of male patients did not change significantly across time. Overall, the number of comorbidities at PD start was higher in more recent cohorts. The duration of follow-up was similar between different yearly cohorts.

Peritonitis rate decreased in more recent incident cohorts. When looking at the causative agents of peritonitis, while the proportion of gram positive and fungal infections remained stable across time, gram negative seemed to increase. The proportion of peritonitis episodes requiring PD tube removal, instead, did not change significantly across time (table 3)

Table 2. Changes in incident PD population and clinical practice across time (Stoke cohort)					
	1990-1994	**1995-1999**	**2000-2004**	**2005-2009**	**2010-2016**
N of patients	170	200	161	127	207
Gender, male	94 (55%)	106 (53%)	82 (51%)	79 (62%)	130 (63%)
Age *	56 (38-66)	60 (50-70)	56 (41-66)	58 (46-70)	65 (52-73)
BMI *	24.9 (4.7)	25.7 (4.8)	27.2 (5.3)	26.9 (5.7)	27.2 (5.2)
Serum albumin, mg/dl*	32 (6)	30 (5)	30 (5)	30 (5)	29 (6)
Urine volume, ml *	350 (0-868)	586 (100-1129)	681 (153-1359)	836 (300-1400)	1167 (665-1585)
Diabetes *	7 (4%)	38 (19%)	48 (30%)	39 (31%)	66 (32%)
Comorbidity score*					
0	78 (46%)	90 (45%)	68 (42%)	46 (36%)	80 (38.5%)
1-2	79 (46.5%)	82 (41%)	72 (45%)	69 (54%)	97 (47%)
>3	12 (7%)	26 (13%)	20 (12.5%)	11 (9%)	29 (14%)
missing	1 (0.5%)	2 (1%)	1 (0.5%)	1 (1%)	1 (0.5%)
First PET timing, days	29 (0-30)	30 (29-59)	41 (29-59)	50 (31-83)	57 (34-95)
Follow-up, years	1.6 (0.5-3.5)	1.3 (0.5-2.8)	1.6 (0.6-3.2)	1.9 (0.7-3.5)	1.0 (0.3-2.0)
Peritonitis rate	1.15	0.67	0.52	0.61	0.34
PD outcome:					
death	51 (30%)	66 (33%)	48 (30%)	34 (27%)	50 (24%)
transfer to HD	49 (29%)	58 (29%)	66 (41%)	55 (43%)	46 (22%)
transplant	60 (35%)	56 (28%)	40 (25%)	25 (20%)	27 (13%)
recover	-	-	-	3 (2%)	5 (2.5%)
lost at follow-up	10 (6%)	20 (10%)	7 (4%)	3 (2%)	1 (0.5%)
still on PD	-	-	-	7 (6%)	78 (38%)
D/P creatinine *	0.62 (0.14)	0.66 (0.11)	0.71 (0.12)	0.79 (0.14)	0.72 (0.18)
Ultrafiltration, ml *	261 (257)	265 (281)	252 (227)	190 (248)	107 (276)
APD *	15 (9%)	26 (13%)	61 (38%)	86 (68%)	180 (87%)
Icodextrin *	7 (4%)	20 (10%)	85 (53%)	85 (67%)	87 (42%)
Dry long dwell *	9 (5%)	6 (3%)	2 (1%)	14 (11%)	108 (52%)
Average daily prescribed glucose concentration, %*	1.86 (1.36-2.27)	1.97 (1.36-2.27)	1.59 (1.36-2.04)	1.37 (1.36-1.82)	1.36 (1.36-1.36)
Biocompatible solutions *	-	-	7 (4%)	7 (6%)	19 (9%)

Table 2: changes in incident PD population and clinical practice across time
Data are expressed as frequency (percentage), median (interquartile range) or mean (standard deviation). Peritonitis rate is expressed as episodes per patient/year.
**Time varying covariates, reported at PD start*

Table 3. Changes in PD peritonitis across time					
	1990-1994	**1995-1999**	**2000-2004**	**2005-2009**	**2010-2016**
N episodes, total	534	370	248	279	251
Causing agent					
Culture negative	170 (33%)	125 (32%)	86 (35%)	88 (31%)	43 (18%)
Gram positive	258 (47%)	153 (43%)	99 (39%)	136 (49%)	114 (45%)
Gram negative	34 (6%)	38 (10%)	30 (13%)	41 (15%)	83 (30%)
Fungal	14 (3%)	3 (1%)	3 (1%)	3 (1%)	3 (1%)
Other not specified	58 (11%)	51 (14%)	30 (12%)	11 (4%)	8 (6%)
PD tube removal	97 (18%)	72 (20%)	45 (19%)	39 (14%)	54 (17%)

Table 3: changes in peritonitis across time (incident and prevalent)
Data are expressed as frequency (percentage).

3.1.2. Changes in clinical practice

Across time, the main differences in clinical practice were related to PD modality, average prescribed glucose concentration and long dwell management.

As regards PD modality, the proportion of APD patients progressively increased from 2004 onward (figure 6).

As regards average prescribed glucose concentration, in older cohorts it was higher at PD start, and increased further during follow-up to achieve ultrafiltration. This changed notably in more recent cohorts, with a lower prescribed glucose both at PD start and during follow up. These changes occurred at a similar time to the increase in urine volume and a greater use of icodextrin and APD (figure 7).

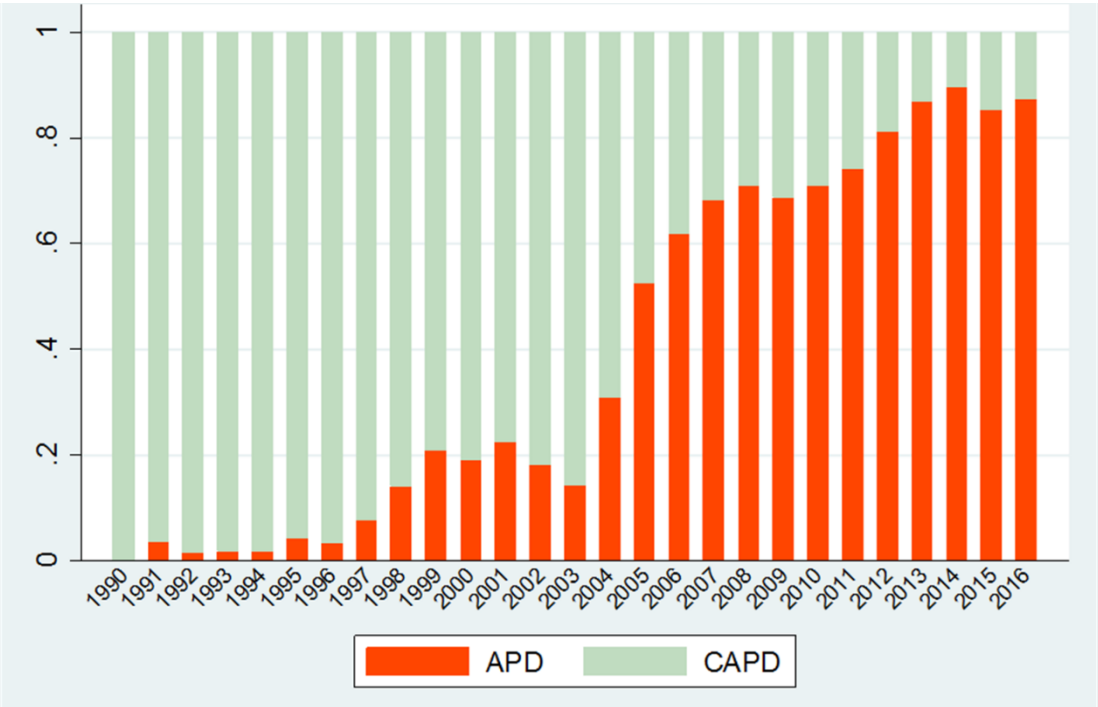


Figure 6: Changes in PD modality over time

Stacked bar graph showing the relative proportion of prevalent APD and CAPD patients treated in Stoke in different calendar years. The proportion of patients treated with APD markedly increased from 2004 onwards, as a result of a change in the centre clinical policy.

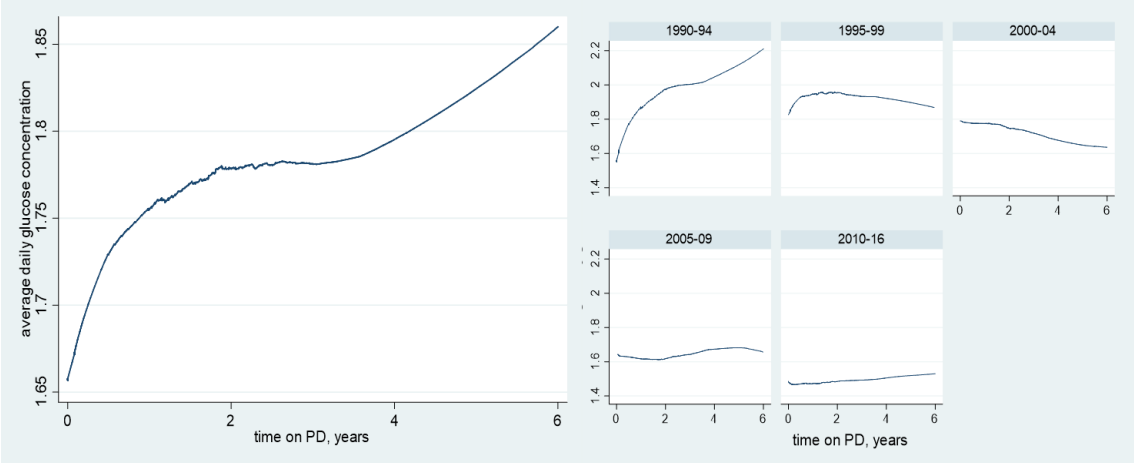


Figure 7: Long term changes in the average daily prescribed glucose concentration

Linear regression of prescribed glucose concentration over years of follow-up on PD, in the overall population (left panel) and in different incident cohorts (right panels).

In earlier cohorts, longer time spent on PD was associated with higher concentration of daily prescribed glucose (most likely to counteract the rise in PSTR occurring during follow up, and subsequent drop in UF capacity). Starting from the early 2000s, instead, the average daily prescribed glucose started to decrease, likely reflecting both the introduction of icodextrin and changes in residual urine volume.

In the management of long dwell, icodextrin gradually replaced 3.86% and 2.27% glucose (almost completely abandoned after 2004 and 2008 respectively). In more recent years, an increasing number of patients had PD treatment overnight and a dry long dwell during the daytime, a choice that reflects average better residual urine volume (figure 8).

Biocompatible solutions were introduced in the early 2000s in a small number of patients, and their use has remained very limited since, restricting the possibility of any meaningful inference on their effect in this cohort.

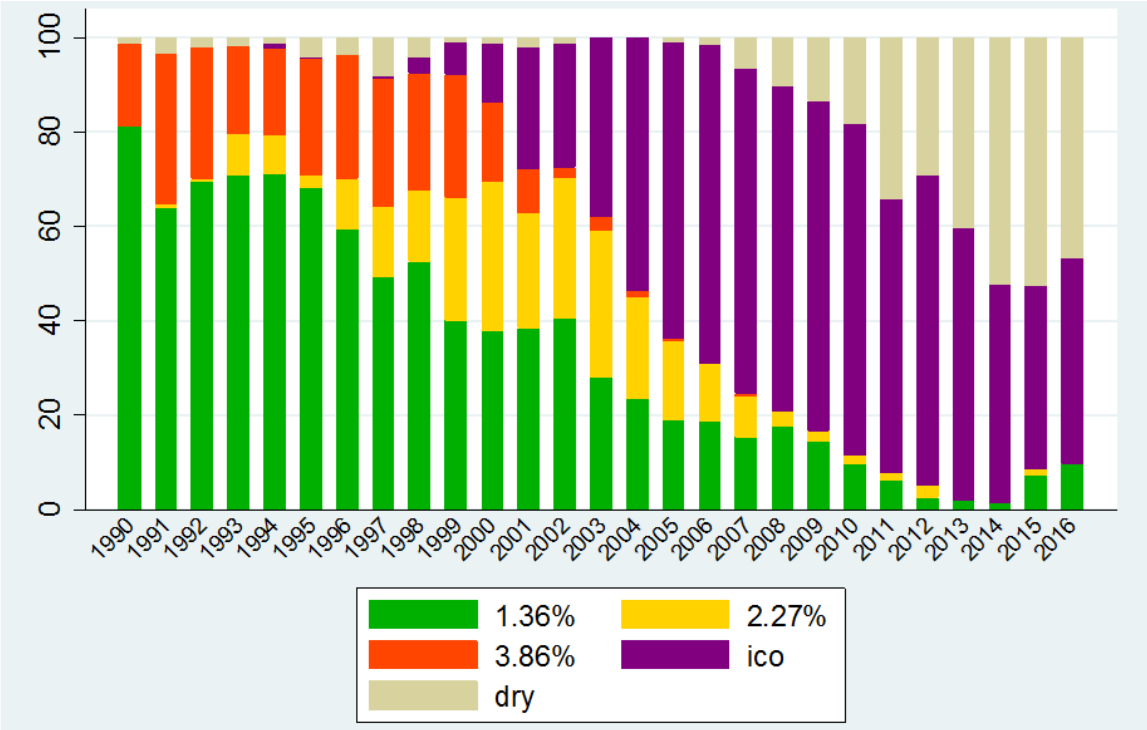


Figure 8: Changes in long dwell strategy over time

Stacked bar graph showing the relative proportion of different PD fluids prescribed for the long dwell in incident patients, grouped by calendar year.

Icodextrin (ico) gradually replaced 3.86% and 2.27% glucose and became the preferred fluid for the long dwell. Moreover, starting from 2006 an increasing number of patients had APD treatment overnight and a dry long dwell during the daytime (dry), likely reflecting an higher average residual urine volume.

3.2 Analysis of peritoneal solute transport rate

As expected, time spent on PD treatment affected the membrane solute transport rate (figure 9). A smoothed curve of individual trends of solute transport rates shows an increase in PSTR over time spent on PD treatment.

When looking at different cohorts (grouped according to the calendar year of PD start), both PSTR at PD start and PSTR rate of increase during follow-up differed significantly between groups, suggesting that changes over time in practice patterns may have driven alterations in PSTR (figure 10).

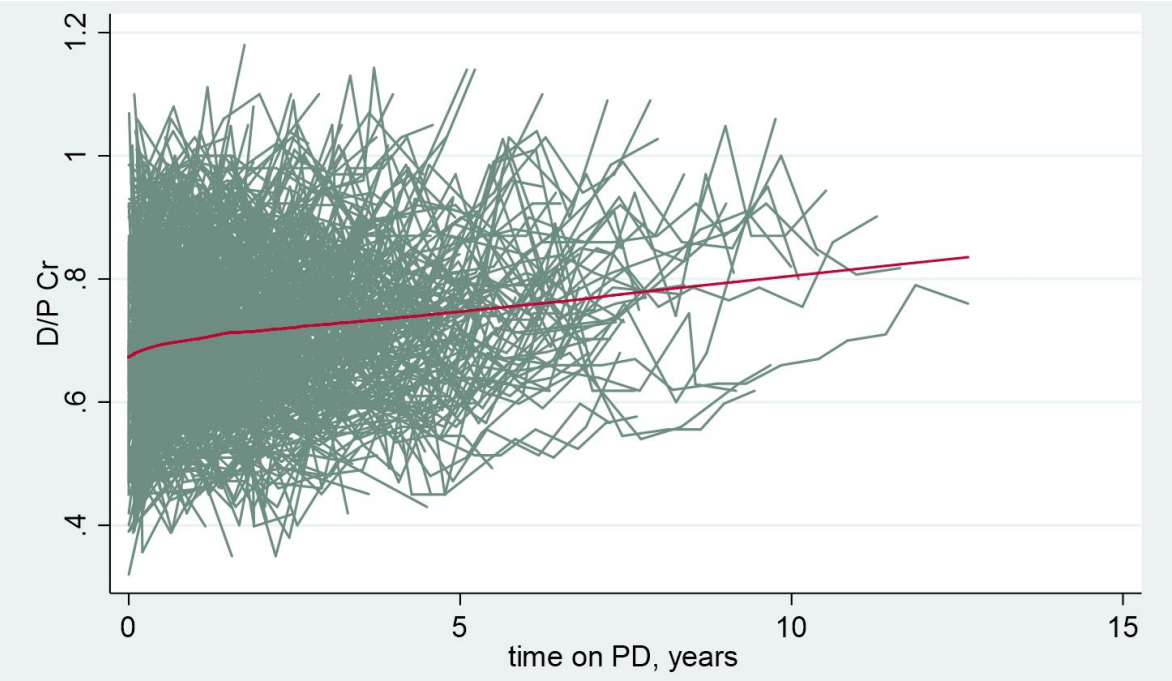


Figure 9: Longitudinal changes in PSTR

Spaghetti plot with individual D/P Cr trajectories over time (blue) and overall trend (locally weighted smoothing, red).

In line with previously published data, PSTR increases with time spent on PD. The trend of increase, with the exception of the first 6 months characterised by higher variability, is linear.

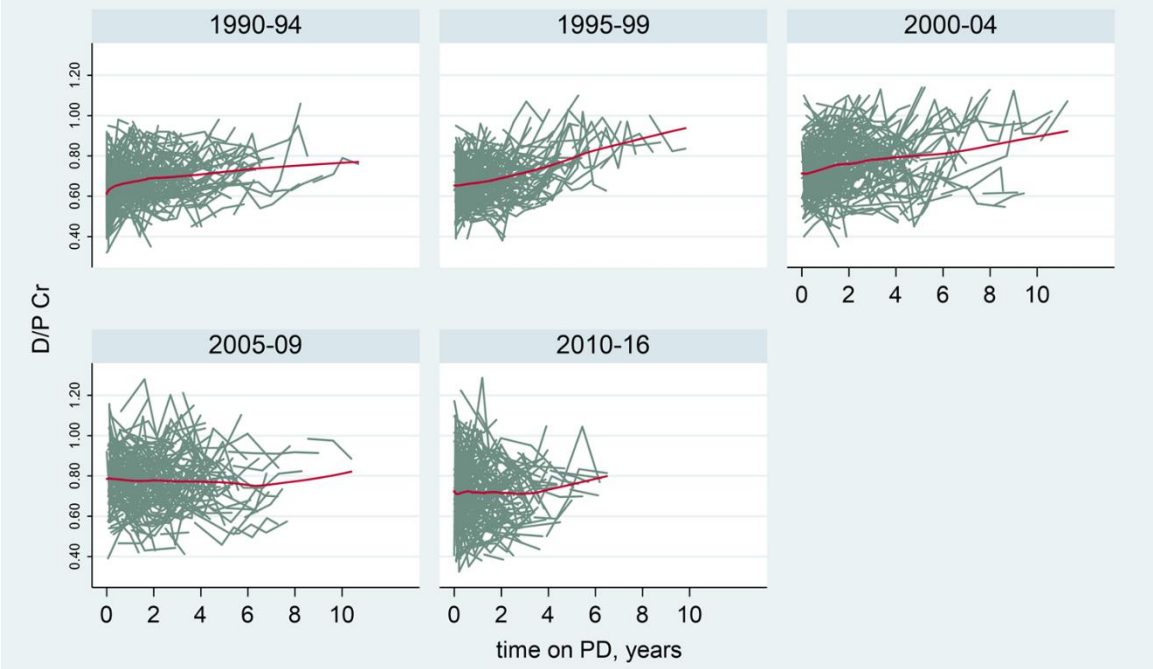


Figure 10: Longitudinal changes in PSTR in different incident cohorts

Spaghetti plot with individual D/P Cr trajectories over time (blue) and overall trend (locally weighted smoothing, red)

Different cohorts of incident patients showed differences in PSTR during follow up. Both the average PSTR at PD start and the trend of increase were different. In particular, average PSTR at PD start gradually increased across time, peaking in the 2005-2009 incident cohort. As regards PSTR change over time, in patients starting PD before 2005 PSTR showed an increase with time spent on PD, whereas in more recent cohorts it showed a flatter trend.

3.2.1 Changes in PSTR at PD start

3.2.1.1 Stoke cohort

Determinants of PSTR at PD start were investigated with multivariable regression and the impact of both patient factors and practice patterns is shown in table 4.

As expected, patient factors like male gender and diabetes were associated with faster PSTR at baseline. Practice patterns were also associated with differences in PSTR at PD start, with the use of both icodextrin or higher dialysate glucose concentrations being associated with faster PSTR, and dry dwells with slower PSTR. The model accounts for about 32% of the variability observed in PSTR at PD start (R-squared 0.3208).

Table 4. Determinants of PSTR at PD start (Stoke)				
PSTR explanatory variables	**Coefficient**	**95%CI**	**p**	**Stand. Coeff.**
gender, male	0.028	0.010, 0.047	0.002	0.104
BMI	-0.004	-0.005, -0.002	<0.001	-0.135
diabetes	0.022	0.001, 0.043	0.044	0.073
residual urine volume, litres	0.026	0.013, 0.039	<0.001	0.145
PET timing from PD start, days	0.001	0.000, 0.001	0.007	0.094
average daily prescribed glucose concentration, %	0.071	0.051, 0.091	<0.001	0.256
icodextrin	0.099	0.064, 0.134	<0.001	0.227
biocompatible solution	-0.007	-0.059, 0.044	0.776	-0.010
dry long dwell	-0.081	-0.123, -0.039	<0.001	-0.275
period of PD start	0.030	0.020, 0.039	<0.001	0.307
1990-94	*Reference group*			
1995-99	0.008	-0.020, 0.036	0.567	0.026
2000-04	0.062	0.032, 0.091	<0.001	0.184
2005-09	0.102	0.067, 0.137	<0.001	0.266
2010-16	0.084	0.039, 0.128	<0.001	0.246

Table 4: Determinants of PSTR at PD start (Stoke)

Regression parameters estimates from multivariable linear regression (R-squared 0.321).
Interaction between calendar time and icodextrin was tested and not significant.
LR test was performed and showed a significant difference in the model fit when including calendar time as a covariate (p<0.001).

Unexpectedly, average PSTR at PD start showed significant differences between patients starting PD treatment at Stoke in different calendar years, and that was confirmed after adjustment for patient factors and practice patterns and significant when tested with likelihood ratio test.

For a graphical display, a scatter of unadjusted individual values of PSTR at PD start, plotted against year of PD start, shows a progressive increase in average PSTR at PD start until 2007, followed by a decrease (figure 11).

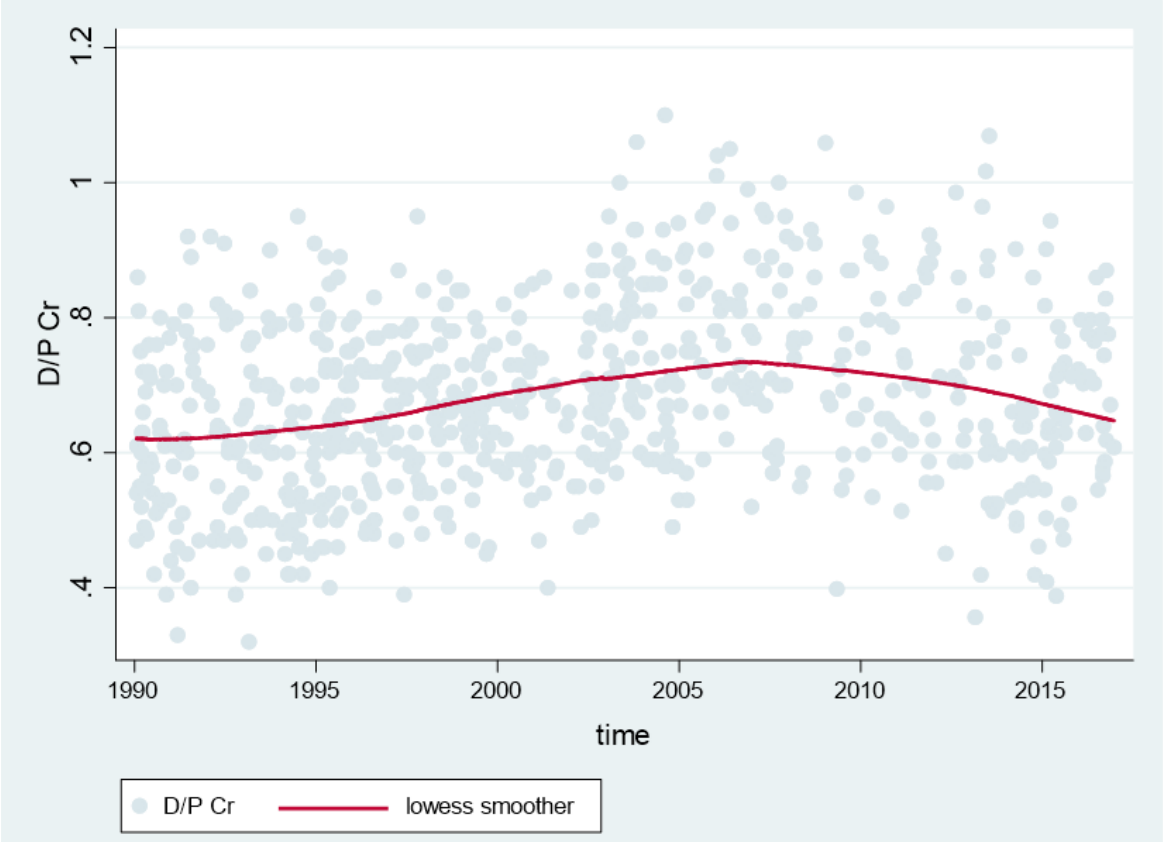


Figure 11: PSTR at PD start across time, Stoke cohort

Scatter plot showing individual PSTR measurement at PD start by calendar year (blue dots) and average trend (locally weighted smoothing, red). Among Stoke PD patients, average PSTR at PD start increased from 1990 until nearly 2007, and subsequently started falling.

3.2.1.2 Global Fluid cohort

As regards PSTR at PD start, a similar trend of increase across time was observed in Global Fluid cohort (figure 12). The pattern was not consistent between countries (figure 13), with the UK showing a greater increase over time when compared to Korea and Canada. This was confirmed after exclusion of patients from Stoke enrolled in the Global Fluid Study.

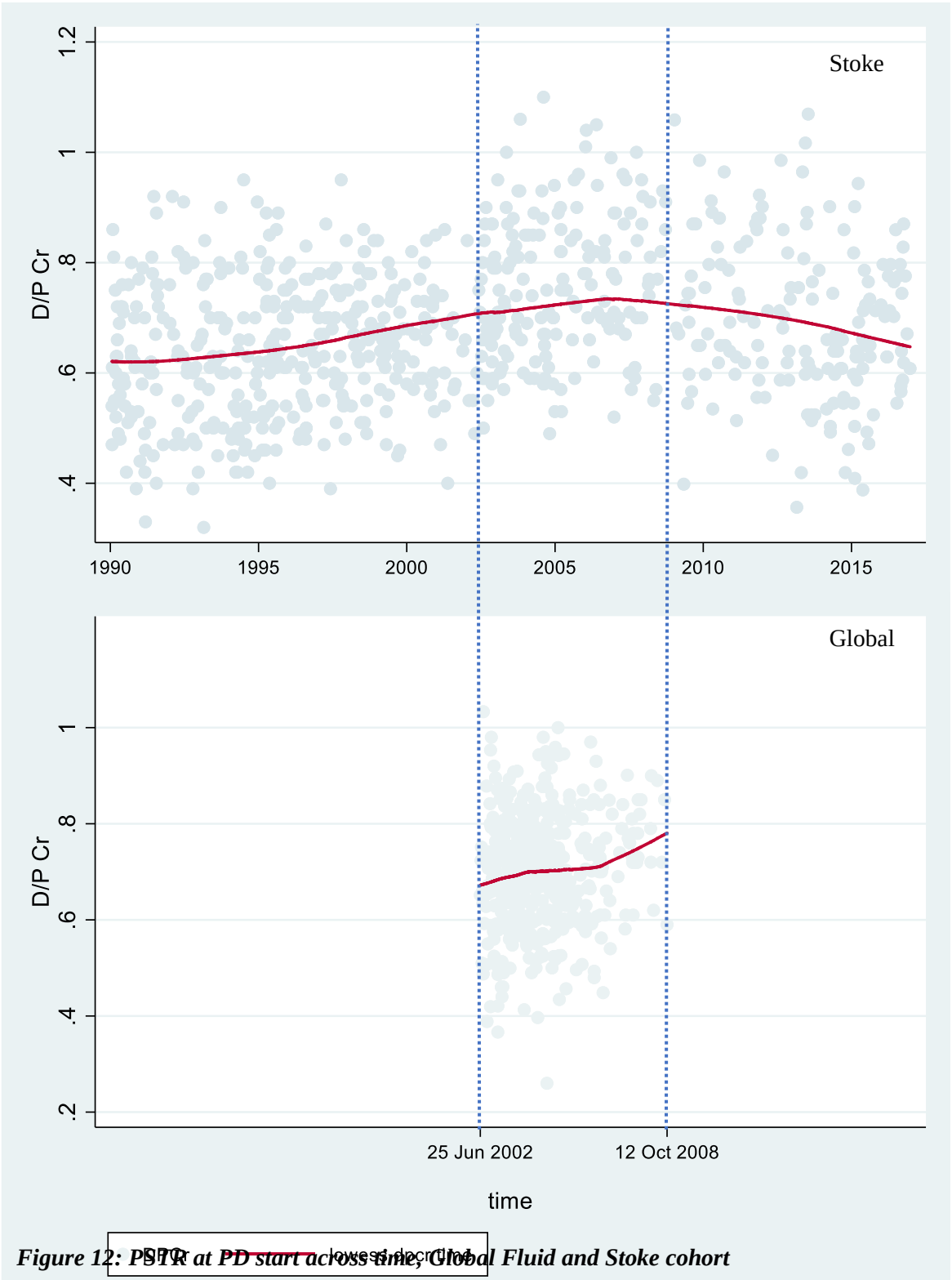


Figure 12: PSTR at PD start across time, Global Fluid and Stoke cohort

Scatter plot showing individual PSTR measurement at PD start by calendar year (blue dots) and average trend (locally weighted smoothing, red) in Stoke and Global Fluid cohort (top and bottom panel, respectively).

Data from the Global Fluid dataset confirm PSTR at PD start is not constant across incident cohorts, but rather increases between 2002 and 2008 (data from Global are shown after exclusion of patients originally recruited from Stoke, to avoid duplication).

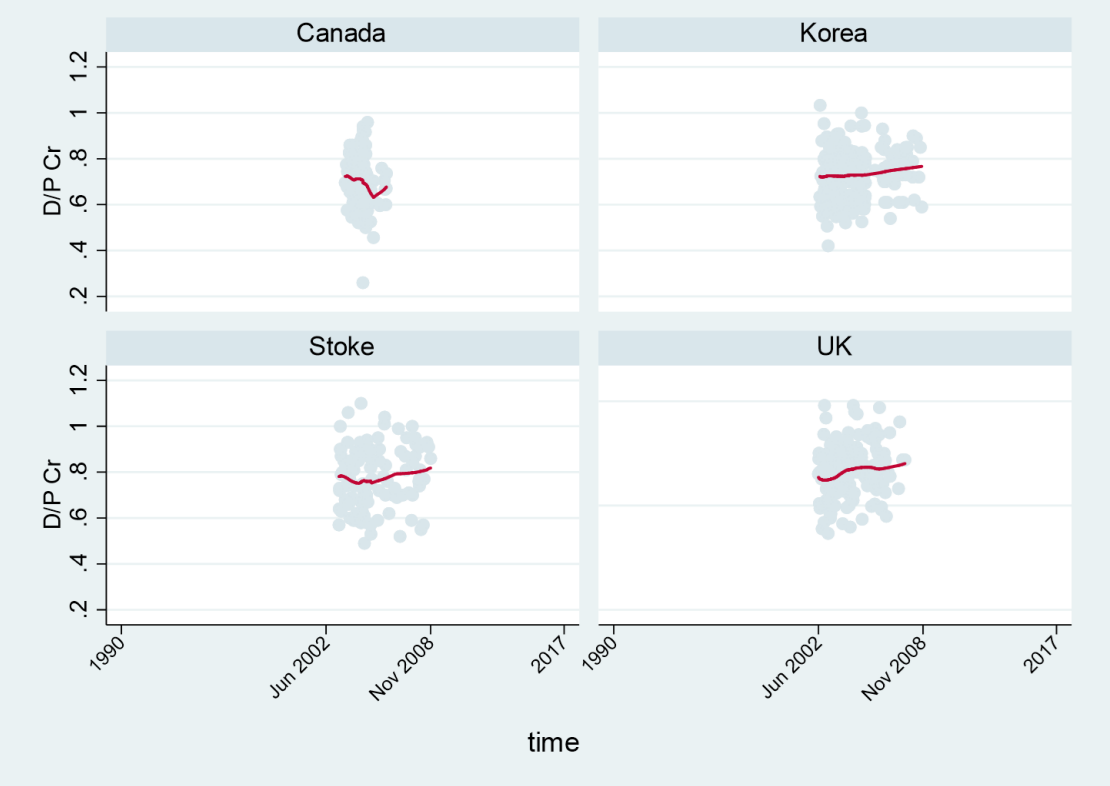


Figure 13: PSTR at PD start in different countries within the Global Fluid cohort

Scatter plot showing individual PSTR measurement at PD start by calendar year (blue dots) and average trend (locally weighted smoothing, red) in different countries within the Global Fluid cohort.

Different countries show a different trend in PSTR at PD start. Data from UK show an increase in PSTR across incident cohorts. UK data are displayed after exclusion of Stoke patients enrolled in Global, shown separately to avoid duplications.

Determinants of PSTR at PD start in the UK cohort were investigated in an exploratory model, using the same covariates previously tested in Stoke (table 5a). Dialysate IL-6 was also added to the model, resulting in an improved model fit for PSTR (table 5b, R-squared 0.389 vs 0.315). Moreover, the estimate for icodextrin was reduced when introducing IL-6, showing a smaller effect on PSTR compared to the preliminary model.

Table 5a. Determinants of PSTR at PD start in UK				
PSTR explanatory variables	**Coeff**	**95% CI**	**p**	**Stand. Coeff**
gender, male	0.032	-0.012, 0.077	0.152	0.118
BMI	-0.004	-0.009, -0.001	0.079	-0.146
diabetes	0.005	-0.039, 0.049	0.796	0.022
residual urine volume, litres	0.028	0.001, 0.055	0.024	0.197
PET timing from PD start, days	0.002	0.001, 0.003	0.032	0.257
average daily prescribed glucose concentration, %	0.011	0.001, 0.019	0.088	0.185
biocompatible solution	0.013	-0.029, 0.055	0.733	0.030
icodextrin	0.126	0.042, 0.211	0.098	0.202
centre	0.001	-0.015, 0.018	0.870	0.043
period of PD start	0.027	0.002, 0.052	0.032	0.175
July 2002 to December 2003	*reference group*			
January 2004 to June 2005	0.041	-0.007, 0.090		0.158
July 2005 to December 2008	0.051	-0.001, 0.102		0.170

Table 5a: Determinants of PSTR at PD start in UK (Global Fluid cohort)

Regression parameters estimates from multivariable linear regression (R-squared 0.315). Analysis of UK population within the Global Fluid cohort (excluding Stoke). Centre variable added to account for patient clustering. LR test was performed and showed a significant difference in the model fit when including calendar time as a covariate (p 0.03)

Table 5b. Determinants of PSTR at PD start in UK, including IL-6				
PSTR explanatory variables	**Coeff**	**95% CI**	**p**	**Stand. Coeff.**
gender, male	0.027	-0.015, 0.070	0.200	0.100
BMI	-0.003	-0.007, 0.001	0.132	-0.119
diabetes	0.010	-0.033, 0.053	0.652	0.036
residual urine volume, litres	0.026	0.001, 0.052	0.058	0.155
PET timing from PD start, days	0.001	0.000, 0.002	0.024	0.254
average daily prescribed glucose concentration, %	0.008	-0.001, 0.017	0.067	0.190
biocompatible solution	0.014	-0.027, 0.056	0.489	0.057
icodextrin	0.047	-0.029, 0.125	0.227	0.142
centre	-0.001	-0.016, 0.014	0.923	-0.010
period of PD start	0.026	0.002, 0.049	0.032	0.165
July 2002 to December 2003	*reference group*			
January 2004 to June 2005	0.030	-0.015, 0.077		0.116
July 2005 to December 2008	0.050	0.002, 0.098		0.169

Table 5b: Determinants of PSTR at PD start in UK, including IL-6

Regression parameters estimates from multivariable linear regression (R-squared 0.389). Addition of IL-6 results in a significantly improved model fit for PSTR. The estimate for icodextrin appears smaller when compared to the preliminary model.

Dialysate IL-6 and PSTR association was confirmed across all countries (figure 14). Dialysate IL-6 at PD start showed a pattern of increase across time similar to PSTR (figure 15).

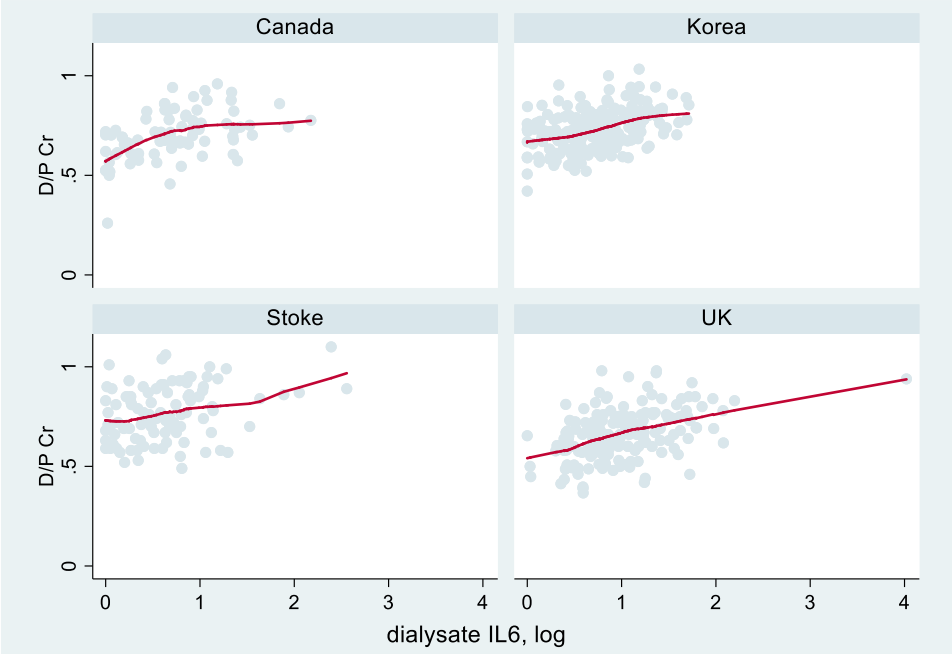


Figure 14: Correlation between PSTR and dialysate IL-6 at PD start

Linear regression of dialysate IL-6 (logarithm of concentration) and D/P creatinine in incident PD patients within the Global cohort, grouped by country of origin. Stoke patients originally enrolled in the Global Fluid study are shown separately.

PSTR and dialysate IL-6 concentration are consistently correlated, suggesting local inflammation might explain part of the interindividual variability observed in PSTR at PD start.

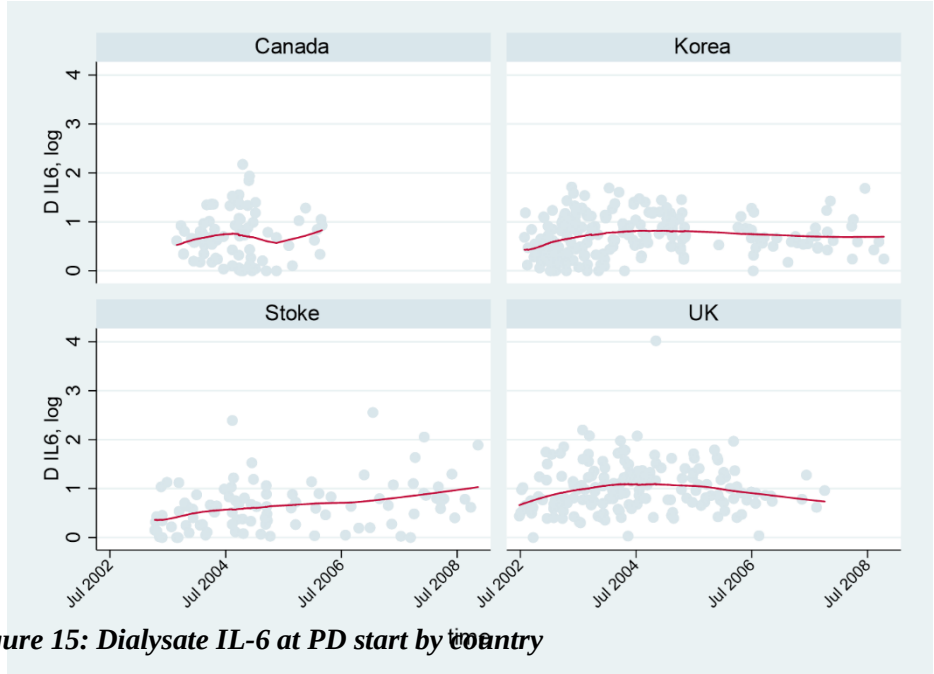


Figure 15: Dialysate IL-6 at PD start by country

Scatter plot of dialysate IL-6 at PD start (logarithm of concentration) by calendar year within the Global cohort. Patients are grouped by country of origin. Stoke patients originally enrolled in the Global Fluid study are shown separately.

The trend in dialysate IL-6 at PD start shows similarities to the trend in PSTR shown in figure 13

3.2.1.3 Cardiff and Swansea cohort

PSTR at PD start showed significant variations within the Stoke cohort across time, the reason behind this phenomenon being not entirely clear. To further investigate the changes observed in this single centre cohort, we analysed Cardiff and Swansea cohorts, who also included data from the early 1990s, a time frame not covered by the Global Fluid cohort.

Average PSTR at PD start showed significant differences between patients starting PD treatment in different calendar years at both Cardiff and Swansea hospital, but no consistency in the patterns was observed nor similarities with the Stoke cohort (figure 16).

Clinical data to correlate with PSTR changes were not available.

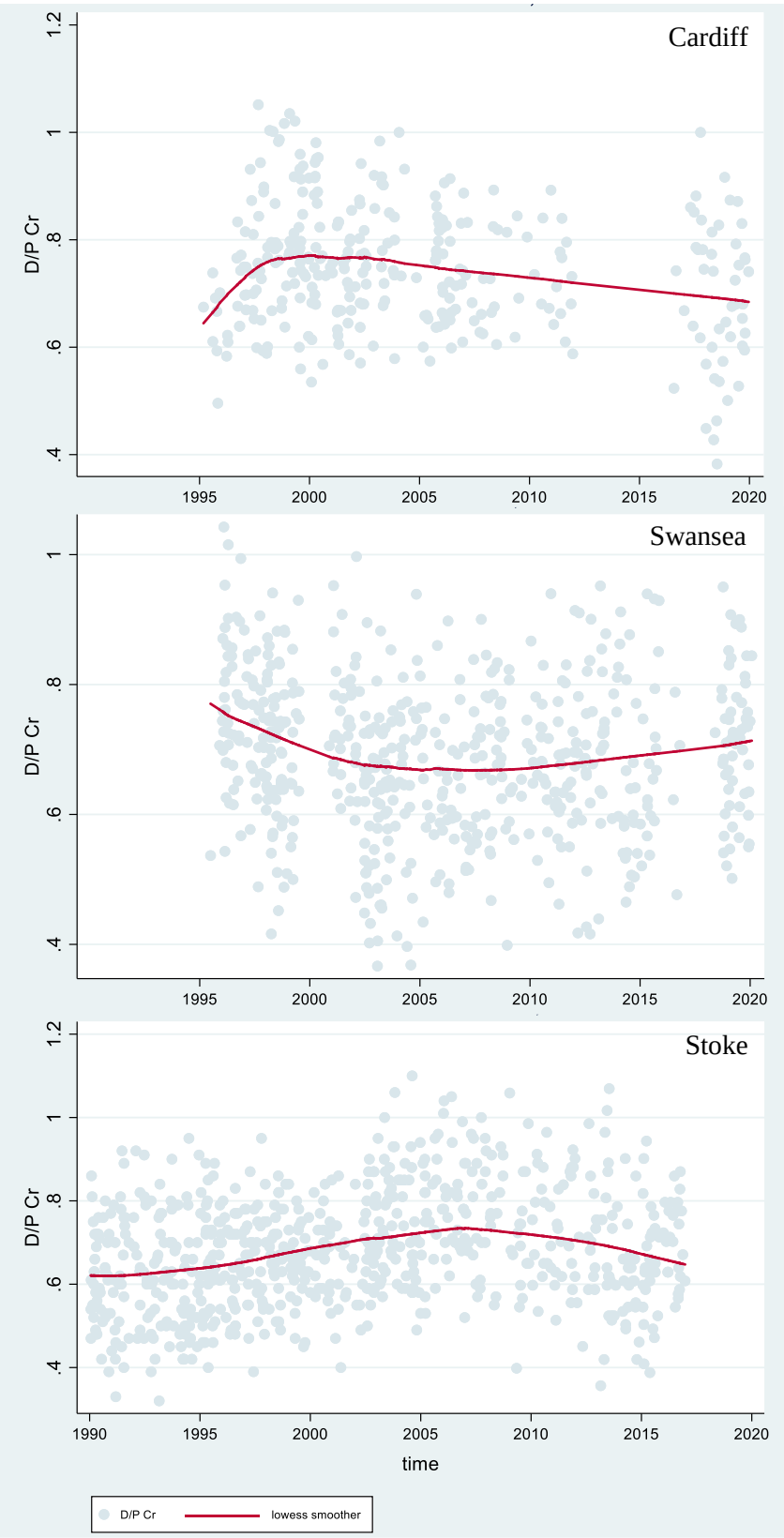


Figure 16: PSTR at PD start across time, Cardiff and Swansea cohort

Scatter plot showing individual PSTR measurement at PD start by calendar year (blue dots) and average (locally weighted smoothing, red).

Average PSTR at PD start changed across time in both Cardiff and Swansea cohorts. No consistency in the trend was observed, nor similarities with the Stoke cohort.

3.2.2 Longitudinal changes in PSTR

The impact of different clinical practice patterns on PSTR was assessed using a linear mixed-effects model, after adjustment for patients' demographics, comorbidities, residual renal function, a period effect, and peritonitis episodes, as shown in table 6. During follow-up, median number of PSTR observations per patient was 3 (interquartile range 2-6).

Table 6. Longitudinal changes in PSTR (Stoke)			
PSTR explanatory variables	**Coefficients**	**95% CI**	**p**
time on PD, years	0.019	0.011, 0.026	< 0.001
gender, male	0.033	0.020, 0.046	< 0.001
diabetes	0.026	0.011, 0.041	0.001
residual urine volume, 100ml	0.001	-0.000, 0.001	0.122
average glucose concentration	0.034	0.026, 0.042	< 0.001
peritonitis episodes	0.002	-0.001, 0.005	0.239
icodextrin	0.044	0.029, 0.058	< 0.001
dry long dwell	- 0.081	-0.105, -0.058	< 0.001
biocompatible solution	- 0.008	-0.029, 0.013	0.478
period of PD start			< 0.001
1990-94	*reference group*		
1995-99	- 0.008	-0.031, 0.014	
2000-04	0.048	0.024, 0.072	
2005-09	0.112	0.085, 0.138	
2010-16	0.086	0.058, 0.115	
Interaction, icodextrin and time	- 0.005	-0.009, -0.000	0.042
Interaction, dry long dwell and time	0.012	0.002, 0.021	0.022
Interaction, period of PD start and time			< 0.001
1990-94	*reference group*		
1995-99	0.002	-0.008, 0.013	
2000-04	0.009	-0.002, 0.019	
2005-09	- 0.022	-0.033, -0.011	
2010-16	- 0.026	-0.039, 0.013	
Variance (slope)	0.0006519	0.0004734, 0.0008977	
Variance (intercept)	0.0073529	0.0063034, 0.0085773	
Covariance (intercept-slope)	-0.0010421	-0.0014349, -0.0006492	

Table 6: longitudinal changes in PSTR (Stoke)
Regression parameters estimates from linear mixed-effects regression analysis.

Covariance between intercept and slope was negative, meaning the overall trend of different slopes in the model was "fanning in" (whereby faster PSTR at PD start was associated with a flatter increase over time, and slower PSTR at PD start showed a steeper increase instead).

Diabetes, male gender and number of previous peritonitis episodes were associated with faster PSTR at any time point during follow-up. Residual urine volume was associated with slower PSTR at any time point when tested in univariate association, but it was no longer significant in the adjusted model.

As regards treatment-related covariates, no significant differences were observed between CAPD and APD patients. Higher glucose concentration in the PD fluid was associated with faster PSTR at any time point, but no interaction with time was observed (figure 17).

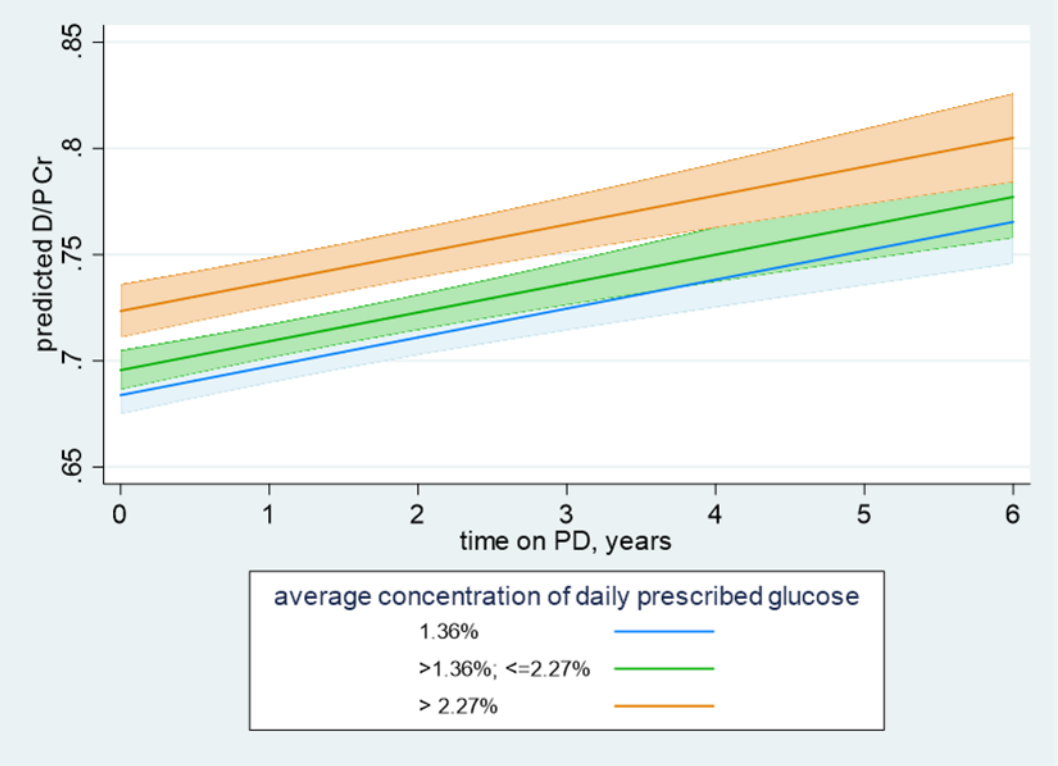


Figure 17: Predicted longitudinal changes in PSTR associated with different average glucose exposure

PSTR is expressed as mean (line) ± 95%CI (area). High concentrations of daily prescribed glucose are associated with higher PSTR at any time point during follow up. Glucose exposure does not affect the slope of increase in solute transport over time.

Different long dwell strategies affected both PSTR starting value and slope. The use of icodextrin was associated with faster PSTR at PD start (0.044, 95% CI 0.029 to 0.058) and slower increase over time (0.012 per year, p=0.022) (figure 18).

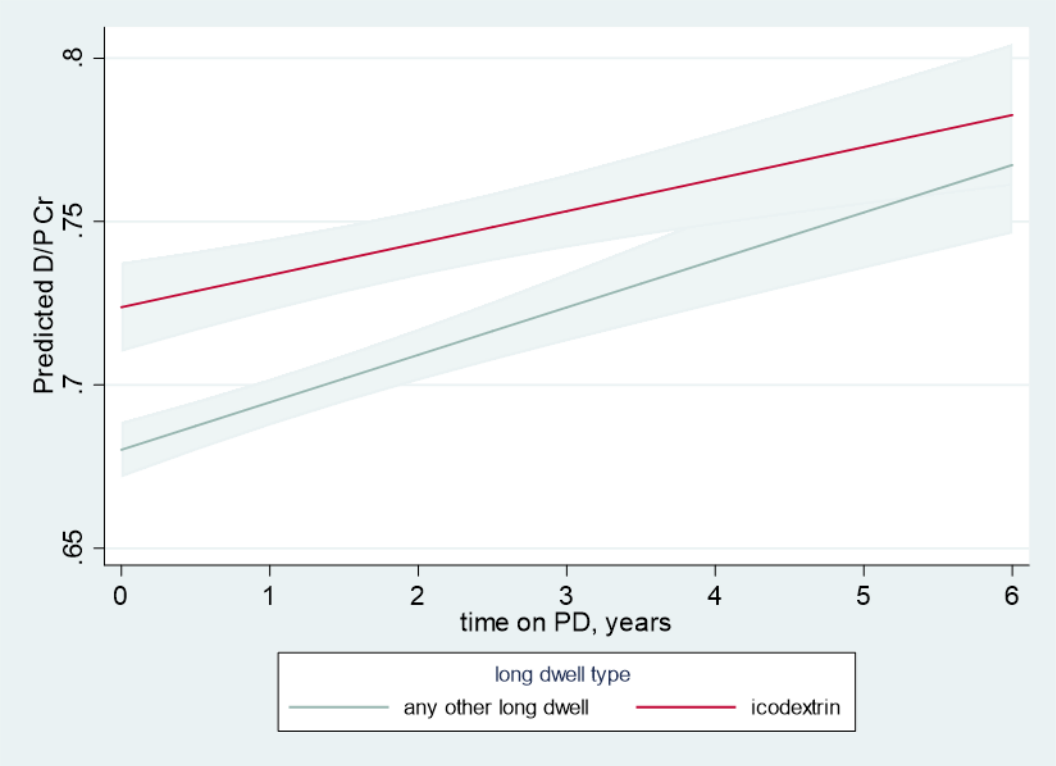


Figure 18: Predicted longitudinal changes in PSTR associated with the use of icodextrin

PSTR is expressed as mean (line) ± 95%CI (area). The use of icodextrin is associated with higher PSTR at PD start but slightly slower increase over time compared to other long dwell types. The association with higher PSTR is likely to represent an indication bias. It is unclear whether the difference predicted in the slope of progression reflects a beneficial effect on PSTR in the long term, rather than a detrimental effect in the initial phase of follow-up, in view of icodextrin pro-inflammatory properties.

Dry long dwells were associated with slower PSTR at PD start (- 0.097, 95% CI -0.122 to -0.073) and faster increase over time (0.029 per year, p<0.022), the overall effect being a PSTR constantly below average after more than 3 years of follow-up (figure 19).

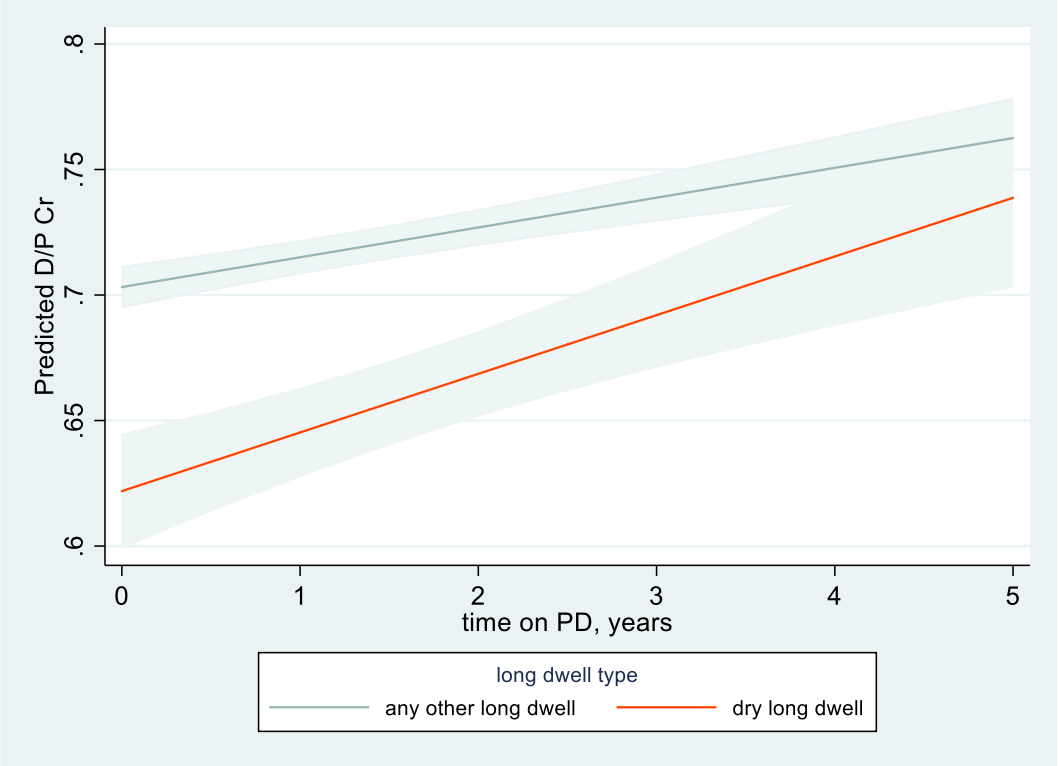


Figure 19: Predicted longitudinal changes in PSTR associated with the use of dry long dwells

PSTR is expressed as mean (line) ± 95%CI (area). The use of dry long dwells is associated with lower D/P Cr at PD start and steeper increase over time. D/P Cr remains below average for more than 3 years of PD treatment.

Different cohorts grouped according to PD start date were characterised by differences in both PSTR at PD start and slope of increase over time. Starting PSTR was significantly slower in the 1990-94 cohort (0.557) and kept then rising until 2005-09 (0.669), before going down again in 2010-16 (0.643). Faster starting values were associated with a flatter increase over time (figure 20).

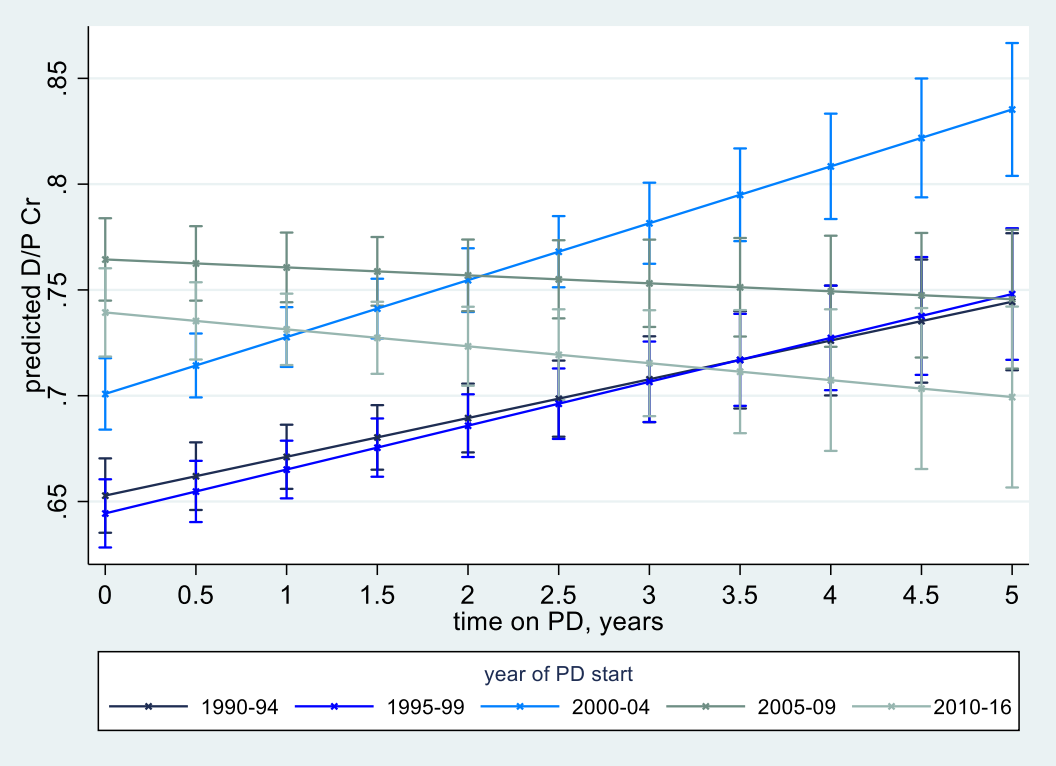


Figure 20: Predicted longitudinal changes in PSTR associated with different years of PD start

PSTR is expressed as mean (line) ± SD (bars). After adjustment for both patient and treatment related covariates, calendar year of PD start is still associated with significant differences in both PSTR initial value and slope of increase over time, likely representing underlying variables not captured by our model

3.3 Survival analysis

In the analysis of PD outcomes using cause-specific hazards regression models, PSTR (analysed as time-varying variable) was associated with both rates of death and transfer to HD (table 7-8, figure 21-22 for a graphical display). The effect estimate was slightly attenuated when other explanatory variables were included in the model.

Table 7. PSTR association with death			
Univariable association			
	HR	**95% CI**	**p**
D/P Cr	1.17	1.066, 1.290	0.001
Multivariable association			
D/P Cr	1.11	0.998, 1.230	0.055
Age, years	1.04	1.027, 1.050	<0.001
Comorbidity Score	1.50	1.351, 1.673	<0.001
Residual urine volume, litres	0.52	0.405, 0.659	<0.001

Table 7: PSTR association with death
Cause-specific hazards regression, death as PD outcome, unadjusted (top) and adjusted for patient-related covariates. 784 subjects, 234 events. D/P Cr and residual urine volume are analysed as time varying variables. Comorbidity score and age are recorded at PD start. Hazards are reported per 0.1 increase in D/P creatinine.

Table 8. PSTR association with transfer to HD			
Univariable association			
	HR	**95% CI**	**p**
D/P Cr	1.34	1.222, 1.476	<0.001
Multivariable association			
D/P Cr	1.30	1.179, 1.442	<0.001
Age, years	0.99	0.990, 1.007	0.702
Comorbidity Score	1.04	0.907, 1.184	0.601
Residual urine volume, litres	0.67	0.546, 0.833	<0.001
BMI	1.04	1.014, 1.065	0.002

Table 8: PSTR association with transfer to HD
Cause-specific hazards regression, transfer to HD as PD outcome, unadjusted (top) and adjusted for patient-related covariates. 784 subjects, 232 events. D/P Cr, residual urine volume and BMI are analysed as time varying variables. Comorbidity score and age are recorded at PD start. Hazards are reported per 0.1 increase in D/P creatinine.

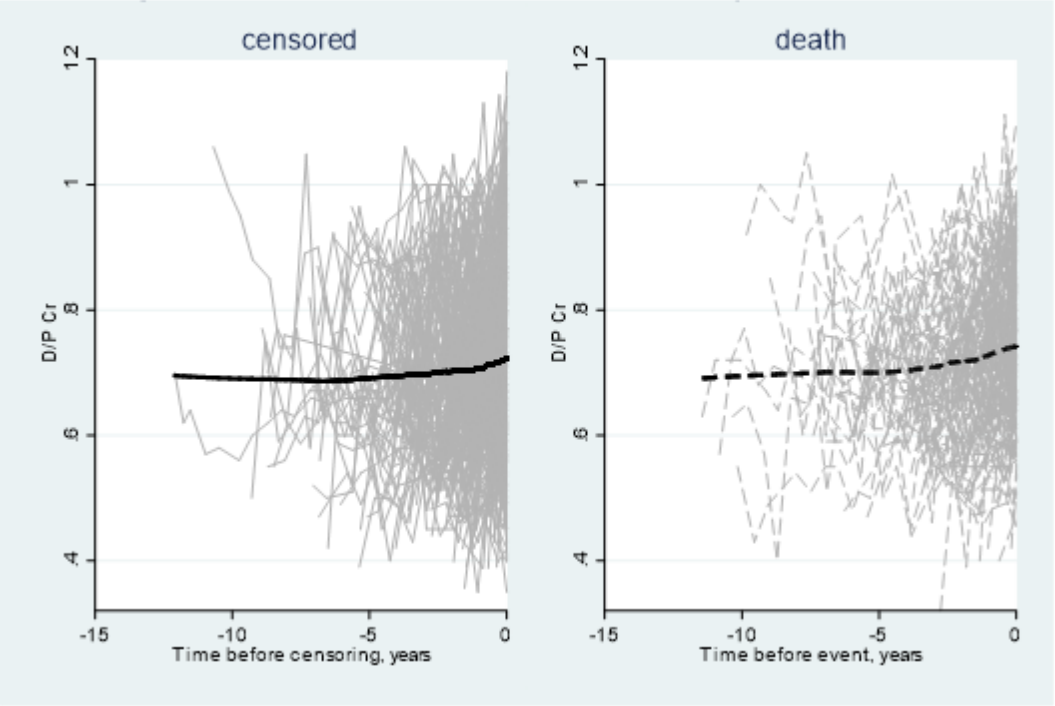


Figure 21: D/P creatinine time course and patient survival

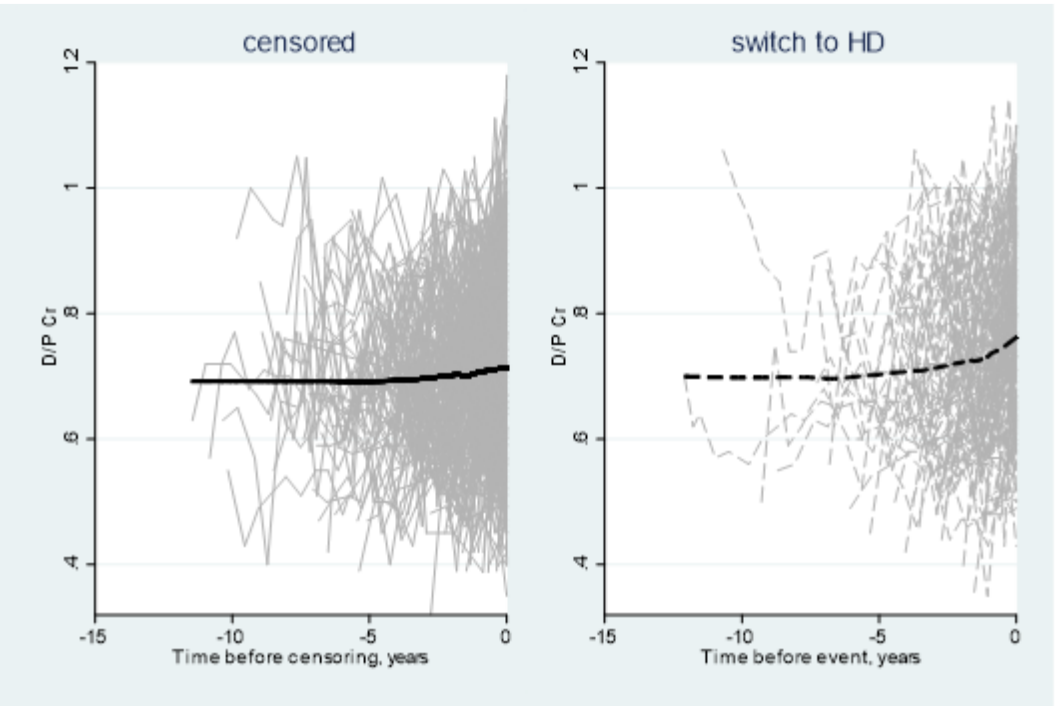


Figure 22: D/P creatinine time course and transfer to HD

To test whether the association between PSTR and outcome changed across time, we compared the estimates for PSTR between different cohorts of incident patients, after adjustment for patient related covariates (age, comorbidities and residual renal function). Death and transfer to HD were analysed as composite outcome. PSTR was included in the regression as time varying covariate. Estimates for different incident cohorts are reported in table 9. The estimate for the 1990-94 cohort is bigger, suggesting a stronger association between PSTR and adverse outcomes in the oldest cohort.

Table 9. PSTR association with adverse outcomes (death or transfer to HD) changed across time

Cohort	N subjects	N events	HR	95% CI	p
1990-94	152	93	1.47	1.213, 1.776	<0.001
1995-99	189	122	1.15	0.967, 1.361	0.117
2000-04	150	105	1.26	1.084, 1.469	0.003
2005-09	111	74	1.28	1.053, 1.547	0.013
2010-16 *	182	72	0.99	0.817, 1.194	0.898

Table 9: PSTR association with adverse outcome changes across time
*Cause-specific hazards regression, risk of death or transfer to HD in different incident cohorts after adjustment for age, comorbidity score, residual urine volume. D/P Cr and residual urine volume are analysed as time variable, age and comorbidity score are reported at PD start. Hazards are reported per 0.1 increase in D/P creatinine. *estimate biased by right censoring*

We then tested the association between PSTR at PD start (analysed as time-invariant) and outcome. The estimate for PSTR was positive for both death and transfer to HD, but confidence intervals were wide and there was no significant association between PSTR at PD start and outcome, both in univariate and multivariate regression (table 10-11).

Table 10. PSTR at PD start association with death			
Univariable association			
	HR	**95% CI**	**p**
D/P Cr	1.09	0.990, 1.190	0.081
Multivariable association			
D/P Cr	1.03	0.926, 1.133	0.636
Age, years	1.04	1.025, 1.047	<0.001
Comorbidity Score	1.57	1.411, 1.745	<0.001
Residual urine volume, litres	0.87	0.718, 1.063	0.176

Table 10: PSTR at PD start association on death
Cause-specific hazards regression, death as PD outcome, unadjusted (top) and adjusted for patient-related covariates. 763 subjects, 236 events. All variables are recorded at PD start and analysed as time invariant. Hazards are reported per 0.1 increase in D/P creatinine.

Table 11. PSTR at PD start association with transfer to HD			
Univariable association			
	HR	**95% CI**	**p**
D/P Cr	1.05	0.959, 1.155	0.283
Multivariable association			
D/P Cr	1.05	0.954, 1.161	0.308
Age, years	1.00	0.989, 1.006	0.572
Comorbidity Score	1.08	0.947, 1.234	0.252
Residual urine volume, litres	0.78	0.642, 0.943	0.011
BMI	1.05	1.019, 1.071	0.001

Table 11: PSTR at PD start association with transfer to HD
Cause-specific hazards regression, death as PD outcome, unadjusted (top) and adjusted for patient-related covariates. 731 subjects, 225 events. All variables are recorded at PD start and analysed as time invariant. Hazards are reported per 0.1 increase in D/P creatinine.

We also tested whether the impact of starting PSTR on outcome may have changed across cohorts by introducing calendar time in the regression. Interaction between PSTR and calendar time was not significant, suggesting the impact of starting PSTR on outcome remained the same across cohorts (table 12-13).

Table 12. PSTR at PD start association with death does not change across incident cohorts

	HR	95% CI	p
D/P Cr	1.15	0.924, 1.435	0.210
Age, years	1.04	1.026, 1.049	<0.001
Comorbidity Score	1.59	1.425, 1.764	<0.001
Residual urine volume, litres	0.91	0.740, 1.113	0.353
Calendar time, years after 1990	1.04	0.929, 1.155	0.528
Interaction between D/P Cr and calendar time	0.99	0.978, 1.008	0.355

Table 12: PSTR at PD start association with death does not change across incident cohorts
Cause-specific hazards regression, 763 subjects, 236 events. All variables are recorded at PD start. Hazards are reported per 0.1 increase in D/P creatinine.

Table 13. PSTR at PD start association with transfer to HD does not change across incident cohorts

	HR	95% CI	p
D/P Cr	1.18	0.952, 1.452	0.132
Age, years	1.00	0.989, 1.006	0.503
Comorbidity Score	1.09	0.950, 1.241	0.224
Residual urine volume, litres	0.76	0.625, 0.933	0.008
BMI	1.04	1.018, 1.072	0.001
Calendar time, years after 1990	1.07	0.964, 1.187	0.203
Interaction between D/P Cr and calendar time	0.99	0.976, 1.006	0.216

Table 13: PSTR at PD start association with transfer to HD does not change across incident cohorts
Cause-specific hazards regression, 731 subjects, 225 events. All variables are recorded at PD start. Hazards are reported per 0.1 increase in D/P creatinine.

Finally, to test whether PSTR rate of increase over time (rather than the absolute value) was associated with PD outcome, a separate model was run using PSTR at PD start and PSTR increase from baseline (analysed as constant and time-varying respectively). PSTR rate of increase was associated with both death and transfer to HD in univariable association. When explanatory variables were included in the model, it was still associated with transfer to HD, but showed no association with death (table 14-15).

Table 14. PSTR at PD start and PSTR rate of increase association with death			
	HR	**95% CI**	**p**
D/P Cr at PD start	1.19	1.070, 1.331	0.002
D/P Cr increase from baseline	1.15	1.035, 1.285	0.010
D/P Cr at PD start	1.11	0.981, 1.250	0.100
D/P Cr increase from baseline	1.11	0.986, 1.250	0.083
Age, years	1.04	1.027, 1.050	<0.001
Comorbidity Score	1.50	1.351, 1.673	<0.001
Residual urine volume, litres	0.52	0.405, 0.659	<0.001

Table 14: PSTR at PD start and PSTR rate of increase association with death
Cause-specific hazards regression, risk of death as PD outcome, unadjusted (top) and adjusted for patient-related covariates. 784 subjects, 234 events. D/P Cr increase from baseline and residual urine volume are analysed as time varying variables. Comorbidity score and age are recorded at PD start. Hazards are reported per 0.1 increase in D/P Cr from baseline.

Table 15. PSTR at PD start and PSTR rate of increase association with transfer to HD			
	HR	**95% CI**	**p**
D/P Cr at PD start	1.28	1.149, 1.425	<0.001
D/P Cr increase from baseline	1.41	1.267, 1.570	<0.001
D/P Cr at PD start	1.26	1.124, 1.418	<0.001
D/P Cr increase from baseline	1.34	1.198, 1.507	<0.001
Age, years	0.99	0.989, 1.007	0.757
Comorbidity Score	1.04	0.910, 1.188	0.568
Residual urine volume, litres	0.68	0.552, 0.844	<0.001
BMI	1.04	1.012, 1.064	0.003

Table 15: PSTR at PD start and PSTR rate of increase association with transfer to HD
Cause-specific hazards regression, risk of transfer to HD as PD outcome, unadjusted (top) and adjusted for patient-related covariates. 784 subjects, 232 events. D/P Cr increase from baseline, residual urine volume and BMI are analysed as time varying variables. Comorbidity score and age are recorded at PD start. Hazards are reported per 0.1 increase in D/P Cr from baseline.

4. Discussion

4.1 Analysis of the Stoke cohort: description of patient level and practice patterns changes over time

Over the past three decades routine clinical practice in PD changed significantly, following new insights in peritoneal physiology and the harm caused by glucose, and innovations brought about by the biomedical industry.

PD population also changed, as a result of both changes that affected the general population, such as the increase in life expectancy and diabetes prevalence, and changes specific to the RRT population, related for example to the increased access to kidney transplant and availability of pre-emptive transplant programs.

To analyse differences in PD practice and population across time, patients were grouped in cohorts according to the year of PD start. Having identified some major changes in the PD prescription policy that occurred at the Royal Stoke Hospital over time, we opted for 5-year cohorts. This approach produced 5 cohorts of similar size and allowed for the comparison between the effect of different PD prescription policies on solute transport, with patients within each cohort being exposed to a broadly similar practice pattern.

PD modality choice changed significantly over time. In Stoke CAPD was widely prescribed between 1990 and 2004, when a switch to APD as preferred technique in incident patients occurred. From then on, APD use progressively increased, involving up to 90% patients by 2016 (a proportion way above UK average, which at the time was around 57% according to the 2015 annual renal registry report).

As regards dialysis fluids and long dwell prescription, at least four different strategies followed one another from 1990 on. From 1990 to 2000 glucose-based solutions were widely prescribed. From the early 2000s, instead, growing awareness of glucose toxicity led to some changes. Biocompatible solutions started being prescribed, and 3.86% and 2.27% glucose solutions were gradually dismissed in favour of icodextrin for the long dwell management. Between 2004 and 2010 the proportion of patients treated with icodextrin rapidly increased, reaching a peak and a plateau at around 70% in 2010.

Alongside changes in PD prescription, residual renal function increased over time in the PD population. This may reflect a different approach in the use of diuretics versus hypertonic glucose to achieve UF, together with the option to switch anuric patients to HD. It may also reflect a trend towards earlier initiation of dialysis over time. From 2010 onwards dry long dwells were prescribed in a wider proportion of PD patients, reflecting better average residual urine volume and probably also increased APD usage.

When looking at the peritonitis rate, it dropped significantly from 1995 onwards, a trend consistent with published data [53]. The relative proportion of causative agents also changed, with gram negative infections seemingly increasing over time, at the expenses of both culture negative peritonitis and other organisms (possibly reflecting better laboratory organism detection, but also accuracy in data recording over time).

4.2 Analysis of PSTR at PD start

Interindividual variability in PSTR at baseline is only partly explained by demographics and comorbidities [41,43,44]. We therefore analysed the impact of different PD prescription strategies on PSTR within 90 days from PD start to try and identify potentially modifiable determinants of PSTR. In particular, we tested the impact of PD modality, prescribed glucose

concentration and long dwell strategy, adjusting for patient related covariates and the use of biocompatible solution.

In our model PD modality did not correlate with PSTR. Higher glucose concentration was associated with faster PSTR, in line with previously published data [13]. Icodextrin was also associated with faster PSTR. While this probably represents an indication bias, it might also reflect the pro-inflammatory properties of the molecule [55,56].

Dry long dwells were associated with slower PSTR, possibly reflecting a reduced exposure to glucose. Data previously published associated residual renal function with slower PSTR [13,52], but this was not confirmed in our analysis. It is therefore unlikely that the association between dry dwells and slower PSTR reflect a better residual renal function in our cohort.

Biocompatible solutions have been associated with complex changes in PSTR in previous studies [23-25], therefore they were included in the regression to adjust for their use, but the coefficients are not reliable, due to sample size limitations.

4.2.1 PSTR at PD start across calendar years in the Stoke cohort

Unexpectedly, the analysis of Stoke PD population showed that PSTR at PD start changed across time, progressively increasing from the early 90s and peaking between 2005 and 2009 before decreasing again.

This was an unexpected collateral finding while investigating the possible impact of clinical practice on PSTR at PD start, and it was confirmed after adjustment for patient and PD related covariates. There are a few possible explanations for this trend. It could reflect undetected differences in laboratory measurement that occurred over time. As detailed in the methods, PSTR assessment is based on creatinine measurement and despite adjusting for

changes in creatinine assays, our model could not account for changes in measurement errors that might occur over time.

Moreover, it could reflect other unmeasured local factors, such as subtle changes in the patient mix that remained undetected or changes in clinical practice, such as consistency in defining and recording PD start date across time. This can lead to significant biases, with PSTR variability being particularly high in the first weeks after starting PD treatment [1].

Finally, it could represent a genuine change in PSTR, and we speculate it could possibly be linked to peritoneal inflammation, triggered by factors that remained undetected by our model and only captured under the generic covariate indicating the year of PD start. Our model did not include data on PD catheter type, timing of insertion and technique, that certainly changed over time and might have contributed to early peritoneal inflammation and elevation in PSTR. Moreover, PD fluid manufacturing is likely to have improved over the past 30 years, leading to unmeasured differences in the pro-inflammatory properties of the fluid itself.

When looking at the changes in PSTR at PD start across time, the overall trend showed interesting analogies with the incidence of EPS in the UK, which seemed to peak in the late 2000s, possibly declining in more recent years. Intraperitoneal inflammation might represent a link between these phenomena, but this hypothesis, although fascinating, is not supported by evidence. Clear data on the incidence of EPS across time is missing. Moreover, the analysis of PSTR at PD start in the Cardiff and Swansea cohorts did not show the same pattern observed in Stoke (as discussed in 4.2.3).

4.2.2 PSTR at PD start across calendar years in the Global Fluid cohort

To overcome the limits of a single centre analysis (potentially biased by local factors, as discussed in 4.2.1) and to test the hypothesis that unmeasured intraperitoneal inflammation

might be responsible for differences in PSTR at PD start across time, we performed a secondary analysis of the Global Fluid Study. The analysis of this cohort, despite covering a shorter time frame of observations, allowed for a multicentre comparison and validation of our single centre results.

Unadjusted data from the Global Fluid cohort seemed to confirm PSTR at PD start changed across time. Some interesting differences were observed at a country level, suggesting local factors may be contributing to the results. The trend in PSTR observed in the UK was in fact similar to what observed in Stoke, while Korea showed a less pronounced increase in PSTR over time (the analysis of data from Canada being limited by a shorter enrolment time).

While genetic differences might be contributing to this result, so can differences in fluid manufacturing, as PD fluids supply depends on local manufacturing sites, that are not shared between UK and Korea. The historical Castlebar incident in 2010 (where the UK PD fluid supply was found to contain bacterial lipopolysaccharide as a result of an undetectable mechanical crack in a sterile fluid container at the Castlebar production site) revealed how critical PD fluid manufacturing can be. It is therefore possible that subtle changes in PD fluid manufacturing over time resulted in differences in its pro-inflammatory properties, contributing to the early changes in PSTR observed across the UK.

4.2.3 Impact of IL-6 on PSTR at PD start

When specifically looking at the UK population within the Global fluid cohort (Stoke excluded), calendar time was associated with differences in PSTR at PD start in the adjusted multivariable regression, therefore confirming the trend initially observed in Stoke in a multicentre cohort.

To test the impact of inflammation on PSTR, we included dialysate IL-6 as an explanatory covariate. As mentioned previously, dialysate IL-6 is a surrogate marker for intraperitoneal

inflammation and correlates with a faster solute transport rate. This was confirmed in our analysis, and consistent across different countries. In the analysis of determinants of PSTR at PD start across UK, accounting for inflammation via inclusion of IL-6 seemed to affect the estimate for the impact of year of PD start on PSTR, which appeared smaller. This reinforced the idea that our initial analysis of the Stoke cohort was not able to detect some determinants of intraperitoneal inflammation changing over time, only captured under the generic time period variable. Interestingly, icodextrin was also affected by inclusion of IL-6 in the model. The use of icodextrin was associated with higher PSTR at PD start, but the estimate for icodextrin was smaller when accounting for inflammation. This suggests that at least part of the association between icodextrin and PSTR could be mediated by intraperitoneal inflammation, with icodextrin triggering early rise in PSTR, besides being associated with elevated PSTR because of its clinical indication.

4.2.4 PSTR at PD start across calendar years in the Cardiff and Swansea cohorts

In trying to validate the results about changes in PSTR at PD start observed in Stoke, one of the limits of the Global Fluid cohort was the relatively short time frame covered by its observations. Patient enrolment for the original study happened between 2002 and 2008, therefore potentially capturing only the tail of the phenomenon we were interested in. To try to overcome this limit, we looked for and sourced further UK PD databases recording PET data from the early 90s. Cardiff and Swansea databases both offered the advantage of a continuous record of PET data from 1995 onwards, covering almost all the time frame previously analysed in Stoke. On the flip side, no clinical data other than PETs results were recorded in these databases, therefore limiting the extent of our analysis.

Interestingly, the analysis of Cardiff and Swansea databases confirmed there have been changes to the starting PSTR over time, but the pattern of these changes was not consistent with those previously observed in Stoke. Data from Cardiff showed PSTR at PD start increased from 1995 and peaked around 2000, before declining steadily. In contrast, data from Swansea suggested PSTR at PD start was higher 1995 and decreased until 2005, when it plateaued.

Some additional considerations must be taken into account when interpreting the first part of both slopes. Both Cardiff and Swansea databases, in fact, lack a clear record of the actual date of PD start for each patient, and the first PET recorded has been assumed to be performed at PD start. As a consequence, early 90s observations may refer to prevalent PD patients, that happened to be already on treatment when both databases were instituted. Based on the mean duration of follow up for PD patients at that time (derived from the analysis of Stoke PD patients, showing a mean follow up of 1.3 years, with interquartile range 0.5 to 2.8), we could expect by 1998 any potential biases generated by the inclusion of prevalent patients in those databases to be negligible. Accounting for that, and ignoring the first part of the slopes, significant differences can still be observed between centres.

Another possible source of bias is represented by laboratory assays accuracy. As previously mentioned, changes in laboratory assays occurred over time may have a significant impact on the estimate of PSTR. No information about laboratory measurement techniques were available as regards Cardiff and Swansea, therefore this type of bias can’t be excluded.

With the limitation mentioned above, the analysis of data from Wales confirmed that PSTR at PD start has not remained stable over time in the UK, but further investigation may be required to understand the determinants of these changes. Furthermore, it confirmed the need

for a very careful approach in trying to generalise observation from a single centre database, as local biases can significantly affect the results.

4.3 Analysis of longitudinal changes in PSTR

PD treatment affects the peritoneal membrane physiology and time spent on PD is a known determinant of PSTR. The analysis of Stoke cohort, providing nearly 30 years of continuous and consistent data collection, allowed for the long-term impact on PSTR of different clinical practice patterns and PD prescription strategies to be assessed and compared.

We specifically analysed the impact on PSTR of PD modality, prescribed glucose concentration and long dwell strategy, adjusting for patient related covariates, peritonitis and biocompatible solution.

4.3.1 Impact of PD modality on PSTR

PD modality choice changed significantly over time, and this might be relevant when analysing solute transport as patient treated with APD are generally exposed to larger volumes of PD fluid (which in turns means potentially higher glucose exposure and bioincompatibility). On the other hand, APD requires less handling of the peritoneal catheter, therefore potentially lower risk of peritonitis. Finally, APD allows patients with faster PSTR to remain on PD, therefore potentially introducing a selection bias in the analysis. In the adjusted model, PD modality did not show any effect on PSTR. This result is in line with data previously published [54] which showed no difference between APD and CAPD. As we expressed glucose exposure as average prescribed concentration, the overall glucose load APD patients were exposed to might be underestimated in our analysis (as total volume of PD fluid was not factored in the calculation).

4.3.2 Impact of glucose exposure on PSTR

Glucose exposure was associated with higher PSTR at any time point during follow-up, the cause-effect relationship between these two variables being unclear. Higher glucose concentrations can in fact be prescribed to try and achieve better UF when PSTR increases, rather than be the trigger for the increase itself. Previous studies showed the rise in prescribed glucose precedes the rise in PSTR [13], suggesting a causal relationship. This has not been confirmed in our analysis, where there is no time lag between the increase in glucose exposure and rise in PSTR, but we could not specifically investigate causality. Interaction with time on PD was also not significant in the model, meaning the increase in glucose exposure did not affect rate of PSTR increase during follow-up.

4.3.3 Impact of long dwell choice on PSTR

As regard different long dwell strategies, we found differences in the rate of progression of PSTR associated with the use of icodextrin and dry days.

Icodextrin was associated with higher PSTR at any time point during follow-up. This is not surprising and might simply reflect an indication bias, with icodextrin being specifically prescribed to achieve UF in fast transporters. Interestingly, in our model icodextrin showed a negative interaction with time on PD, meaning that patients treated with icodextrin might have a higher PSTR at PD start, but a slower progression during follow up. Whether the overall effect of icodextrin on PSTR reflects the proinflammatory properties of the molecule [55,56], pushing the starting PSTR up, or the beneficial effect of a glucose-sparing solution, causing a flatter increase over time, is not straightforward. As previously shown, in fact, glucose concentration itself, despite being consistently associated with faster PSTR, does not seem to affect the slope of the fitted PSTR curve. Moreover, further doubts arise when looking at patients undergoing a dry day dwell. These patients, in fact, despite being administered a similar amount of glucose as icodextrin patients, showed a different pattern

of solute transport during PD, characterized by a markedly slower PSTR at PD start but a steeper slope of increase during follow up, the overall effect being a PSTR below average for more than 3 years after PD start (further follow up data analysis being limited by sample size in our model).

4.3.4 Impact of biocompatible solutions on PSTR

Biocompatible solutions have been associated with complex changes in PSTR in previous studies [23-25], therefore they were included in the regression to adjust for their use. The estimate for biocompatible solutions suggests they might be associated with lower PSTR, but this was highly uncertain, as the coefficients are not reliable due to sample size limitations (only 4% of patients, accounting for 5% of the analysed PETs).

4.3.5 Impact of residual renal function on PSTR

Residual urine volume is known to correlate with PSTR [13,52] therefore was included in the analysis. It was associated with lower PSTR at any time point in the preliminary model, but lost its significance after sensitivity analysis. Given the fact icodextrin and dry day patients significantly differ in terms of residual renal function, we tested the effect of residual renal function on PSTR slope of progression using a time interaction variable, but we found no evidence that urine volume affects PSTR slope in our model.

4.3.6 Limitations of the analysis and final considerations

Finally, it is worth noticing that the differences in the progression of PSTR initially observed between cohorts of patients starting PD in different calendar years remained significant in the adjusted model. This suggests the changes in PD population and clinical practice included in our analysis only partially explained this phenomenon, and some more determinants of it remained undetected (and only captured by the generic variable defining the time of PD start).

4.4 Survival analysis

PSTR is not only a marker of peritoneal transport, but also an important predictor of both patients and technique survival [4,49]. Practice patterns have evolved over time, partly driven by the need to manage fluid balance in patients with fast PSTR. We wanted to test whether the relationship between PSTR and adverse outcomes remained stable across time, or whether it changed possibly as a consequence of changes in practice.

We firstly analysed the relationship between PSTR and outcome in the Stoke PD cohort, and we confirmed that PSTR absolute value (when analysed as a time varying covariate, therefore testing multiple measurement per patient) was associated with both patient survival and transfer to HD, after adjustment for age, comorbidities and residual renal function.

We then tested whether the association between PSTR and adverse outcomes changed across time. We decided to analyse death and transfer to HD as a composite outcome, as we believe over time practice may have changed with regards to the decision whether to transfer patients to HD (potentially favouring one or the other adverse event in different annual cohorts), and our focus was on the impact of PSTR on the overall rate of adverse outcomes, and not the relative balance between the two. The comparison of PSTR estimates in different cohorts seemed to indicate the association between fast PSTR and adverse outcomes was stronger in older cohorts, particularly in the 1990-94 cohort where use of APD was extremely limited and icodextrin was not available. This could indicate that differences in the clinical management of fast transporters that occurred over time may have had a positive impact on survival, in line with a metanalysis previously published [4], suggesting the association between PSTR and mortality is strong in CAPD patients and less prominent where APD

treatment is readily available (possibly as a consequence of a more effective management of fluid balance).

PSTR at PD start showed significant differences across incident cohorts in the Stoke cohort. We therefore analysed the impact of starting PSTR on outcome, and whether this association remained constant across time. In cause-specific hazard regression the estimate for PSTR at PD start (analysed as time invariant, therefore testing one measurement per patient) was positive for both death and transfer to HD, but confidence intervals were wide and the association with outcome was not statistically significant, particularly after adjustment for comorbidities, age and residual renal function. An interaction covariate was introduced in the regression to assess whether the association between PSTR at PD start and outcome was different across incident cohorts, but the hypothesis was rejected. The lack of evidence for an association between PSTR at PD start and outcome in the Stoke cohort is possibly secondary to the reduction in statistical power in our sample when analysing only one PSTR measurement per patient, as Mehrotra e al. [49] were previously able to show a significant association between PSTR at PD start and outcome, being able to include in their analysis more than 10000 incident patients (over ten times our sample size).

Finally, seeing as in the longitudinal analysis of PSTR different subsets of patients showed different slopes of PSTR progression (i.e., dry day patients compared with icodextrin), we tested the hypothesis that PSTR increase from baseline (and not just the absolute value) could inform an individual's risk of death or switch to HD. PSTR was therefore decomposed into a baseline value (time-invariant) and difference from baseline (time-variable). Both were associated with death and transfer to HD in the Stoke cohort, suggesting the slope of PSTR change over time is associated with adverse outcomes (a result not shown before in the published literature).

5. Conclusions

Over the past thirty years, both PSTR PD start and PSTR rate of increase over time changed among PD patients treated at the Royal Stoke hospital.

Changes in PSTR at PD start were confirmed in a larger multicentre UK cohort, and are linked to differences in early intraperitoneal inflammation, possibly triggered by PD fluid intrinsic properties changing over time.

Changes in the rate of PSTR increase during follow up are partially explained by different PD prescription strategies. The use of icodextrin and the choice of dry dwells are both associated with potentially beneficial effects on PSTR, the underlying mechanism being still unclear.

PSTR remains an important predictor of both patients and technique survival in our analysis, and different prescription strategies may affect the strength of this association and reduce the risk of adverse outcomes.

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List of abbreviations

AGEs: Advanced Glycation End-Products

APD: Automated Peritoneal Dialysis

CAPD: Continuous Ambulatory Peritoneal Dialysis

Dt/D0: ratio between concentration at time t (4h in standard PET) and concentration at time 0

D/P Cr: ratio between dialysate and plasma Creatinine concentration

DALYs: Disability-Adjusted Life Years

ESRD: End Stage Renal Disease

EPS: Encapsulating Peritoneal Sclerosis

GDPs: Glucose Degradation Products

HD: Haemodialysis

IL-6: Interleukin 6

MTAC: Mass Transfer Area Coefficient

PD: Peritoneal Dialysis

PET: Peritoneal Equilibration Test

PSTR: Peritoneal Solute Transfer Rate

RRF: Residual Renal Function

RRT: Renal Replacement Therapies

TGF-β: Transforming Growth Factor β

UF: Ultrafiltration

UFF: Ultrafiltration Failure

VEGF: Vascular Endothelial Growth Factor

σ (sigma): Osmotic reflection coefficient

Appendix

Table A1: Clinical features of incident PD patients in Global Fluid Study	
N of patients	575
Age	55.6 ± 15.3
Gender, female (%)	38.4
Korean ethnicity (%)	37.2
BMI	25.2 ± 4.7
Total volume of dialysate, l	7.96 ± 1.29
Blood pressure, mmHg	136 ± 21/80 ± 12
Median duration of PD, days	40 (28,55)
PSTR	0.71 ± 0.12
Ultrafiltration capacity, ml	
High glucose (4%)	696.9 ± 18.4
Medium glucose (2.5%)	229.3 ± 17.6
Serum albumin, mg/dl	35.0 ± 5.2
Haemoglobin g/dl	11.0 ± 2.2
Median urine volume, l	0.90 (0.46, 1.44)
Biocompatible solution use (%)	19.3
Icodextrin use (%)	19.1
APD use (%)	6
Comorbidity Score (%)	
Low (0)	35.6
Intermediate (1-2)	56.8
High (>2)	7.6

Table A1: clinical features of incident PD patients in the Global Fluid Study (adapted from [35])

Data are expressed as proportion, mean and standard deviation or median and interquartile range.