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Renal effects of SGLT2 inhibitors in cardiovascular patients with and without chronic kidney disease: focus on heart failure and renal outcomes

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Abstract
The kidney has a prominent role in maintaining glucose homeostasis by using glucose as a metabolic substrate. This occurs by generating glucose through gluconeogenesis, and by reuptaking filtered glucose through the sodium–glucose cotransporters SGLT1 and SGLT2 located in the proximal tubule. In recent studies, the administration of sodium–glucose cotransporters inhibitors demonstrated that inhibition of renal glucose reabsorption significantly reduces adverse renal events and heart failure exacerbations, in type 2 diabetic patients with and without cardiovascular damage as well as in advanced chronic kidney disease and heart failure patients with reduced ejection fraction with and without diabetes. The benefit was consistent throughout the different investigated clinical conditions, ameliorating overall patient outcome. The efficacy of sodium glucose cotransporters inhibitors was prominently linked to the limitation of renal damage as highlighted by the significant reduction on global mortality achieved in the studies investigating diabetic and not diabetic populations with advanced chronic kidney disease. Both studies were halted at the interim analysis because of unquestionable evidence of treatment benefit. In current review, we examine the role of SGLT2 and SGLT1 in the regulation of renal glucose reabsorption in health and disease and the effect of SGLT2 inhibition on clinical outcomes of populations with different cardiovascular conditions investigated with large-scale outcome trials.

Keywords Cardiovascular death · Heart failure · Renal function · Sodium-glucose co-transporter 2 inhibitors · Type 2 diabetes mellitus

Introduction

The concept that the liver is the exclusive site of glucose production in humans in the postabsorptive state has been overcome by large newer evidence. Many laboratory investigations have indeed documented production of glucose by the human kidney in the postabsorptive state, and it is today well accepted that the kidney plays a major role in glucose homeostasis.

Kidney is involved in the regulation of glucose via gluconeogenesis, the de novo synthesis of glucose from non-glucose precursors, glycogenolysis, from breakdown of glycogen and by reabsorbing glucose from the glomerular filtrate [1]. The evidence is strong enough to have reshaped

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the common understanding of glucose cycle and its role in cardiovascular disease pathophysiology and management.

The function of sodium glucose co-transporters SGLT1 and SGLT2 in normal kidney

In healthy adult humans, the maximum renal glucose reabsorption capacity (transport maximum reabsorption of glucose, TmG) is approximately 375 mg per minute, and slightly higher in males than in females [1]. In normal subjects, the glucose filtering speed (approximately 180 g per day equal to about 125 mg per minute) is considerably lower than the TmG, and this explains why glycosuria is not is present in early hyperglycemic condition. In diabetic patients, however, filtered glucose can exceed the tubular reabsorption threshold and lead to glycosuria [1].

The mechanism that allows the kidney to reuptake the glucose present in the glomerular filtrate is based on the coupled and integrated function of glucose transport and sodium (Na +) concentration in the kidney tubule. The Na + glucose reuptake process takes place in the basolateral membrane by activation of Na + glucose co-transporter 2 (SGLT2), associated with the glucose transporter GLUT 2, and glucose co-transporter 1 (SGLT1) associated with the glucose transporter GLUT1. The energy supporting this process is provided by the cell membrane oxygen dependent Na + -K + pump ATPase (Fig. 1 a and b) [1–3].

When the intracellular glucose concentration increases adequately, Na + , together with glucose, passively moves from the cell to the interstitial space, thanks to the facilitation provided by SGLT2 and SGLT1. In this phase, the Na + and glucose ratio is maintained 1:1 for SGLT2 and 2:1 for SGLT1 [1, 3] (Fig. 1b).

The largest proportion of the filtered glucose (80–90%) is reabsorbed via the co-transporter enzyme SGLT2 which is located just below the Bowman's capsule, at the beginning of the S1 segment of the proximal tubule, while the remainder 10–20% is reabsorbed by the SGLT1 co-transporter which is located more distally in the tubule (Fig. 1a). The action of the SGLT2-SGLT1 co-transporters is complementary and aimed at preventing the loss of glucose in the urine. The SGLT2s work with high transport capacity, but with lower affinity for the glucose molecule, while SGLT1s have lower glucose transport capacity, but higher binding affinity so it is available for recovering glucose that SGLT2s have not reabsorbed earlier. In the physiology of the normal subject, however, SGLT1s exert a glucose recovery action markedly lower than the maximum transport capacity they are equipped with [4].

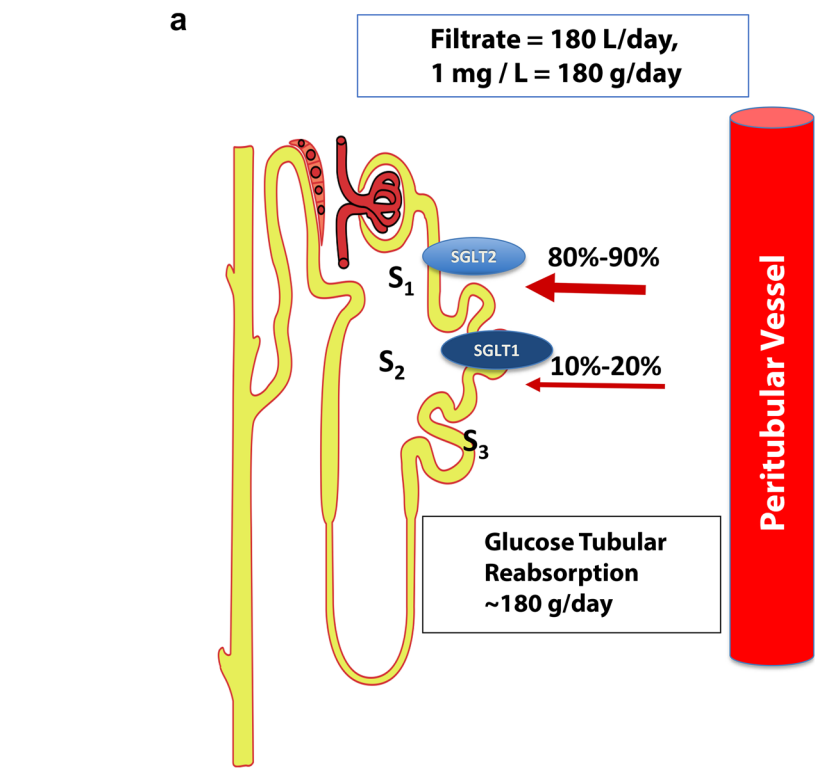
Fig. 1 **a**, **b** (**A**) The kidney is an organ that promotes glucose sparing. In healthy adult humans, the kidney filters about 180 g daily. The filtered glucose is prematurely reabsorbed in toto (180 g/day) and glycosuria does not appear. The mechanism that allows the kidney to recover the glucose present in the glomerular filtrate is based on the coupled and integrated function of glucose and Na + transport from the peritubular vessel to the renal tubule. This mechanism benefits from the action of the sodium-glucose co-transporter type 2 (SGLT2) located in the tubule just below Bowman's capsule in segment S1, associated with the sodium-glucose co-transporter type 1 (SGLT1) located in the underlying segment S2–S3. Eighty to 90% of the filtered glucose is reabsorbed by the SGLT2 enzyme and the remaining portion by the SGLT1 enzyme. (**B**) Glucose sparing in the kidney occurs via reabsorption in the proximal tubule. The action of the SGLT2-SGLT1 cotransporters is complementary, aimed at preventing glucose loss with urine. The reabsorption capacity of the co-transporters is higher than the activity they normally perform. In particular, the presence of a higher concentration of glucose in the filtrate leads to an increase in the activity of the co-transporter SGLT1, which has a high affinity for glucose, leading to an increase in the threshold of glycosuria. The figure shows how the coupling of SGLT2 and SGLT1 with the reciprocal glucose transporter GLUT2 and GLUT1, compose a single mechanism, functional to the complete recovery of glucose present in the filtrate. This mechanism is coupled to Na + recovery, maintaining a glucose to Na + ratio of 1:1 for SGLT2 and 1:2 for SGLT1. Energy for reabsorption of molecules is provided by the Na + /K + ATPase-dependent pump that is located in the basolateral membrane of the tubule. [2] Reproduced with permission from Gronda et al.

Since the reabsorption of Na + and glucose is coupled in the tubule, the increase in glucose reabsorption during hyperglycemia is associated with the increase in the Na + content in the body. The mechanism makes clear kidney glucose handling is strictly connected with body sodium homeostasis and therefore with circulation balance.

Such mechanism represents a key issue in understanding why SGLT2 inhibitors are so effective in decreasing heart failure (HF) exacerbation in the largest spectrum of cardiovascular conditions including diabetic and not diabetic subjects, with and without chronic kidney disease, HF patients with reduced (HFrEF), or preserved ejection fraction (HFpEF).

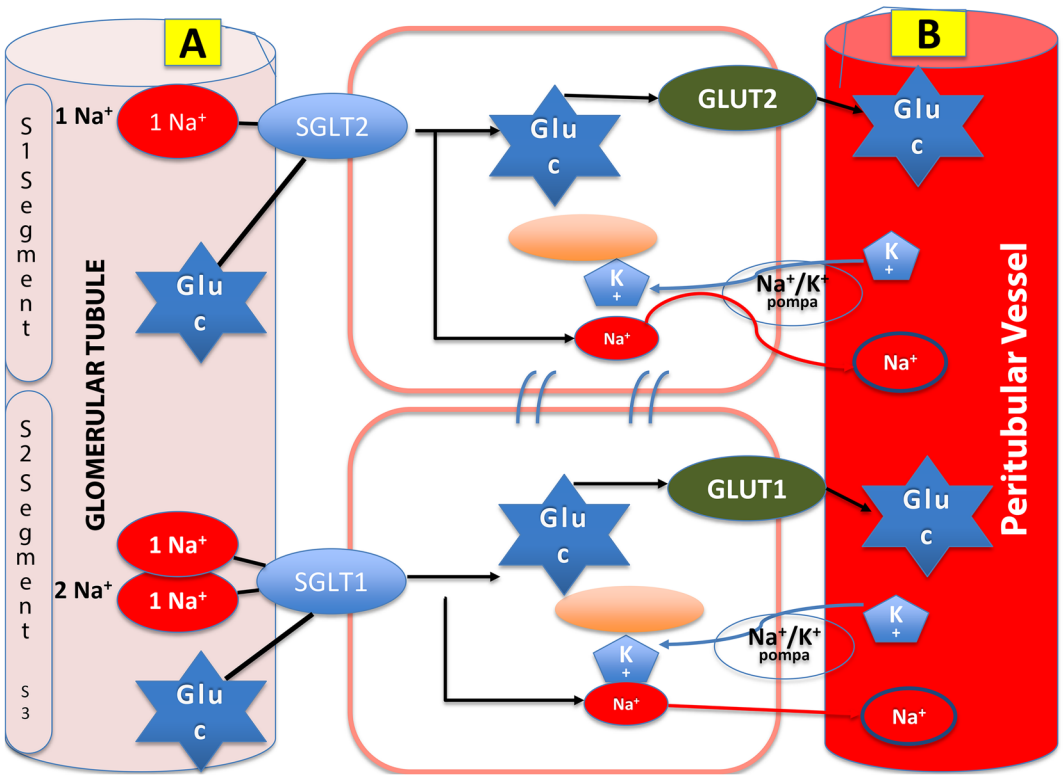
The interplay between hyperglycemic status and sodium glucose co-transporters activity

It's noteworthy to remind in the renal filtrate Na + handling represents an essential physiologic function in mammal for body fluid maintenance and blood pressure balance. Ninety-nine percent of filtered Na + is reabsorbed along the transit in the glomerular tubule. Approximately 50 to 60% of Na + reuptake occurs in the early portion of proximal tubular tract where SGLT2 and SGLT1 are located, 30 to 40% in the thick ascending limb and the remnant in the distal convolute tubule.



Gronda E et al G Ital Cardiol 2021;22(4)

b Glucose Reabsorption Pathway in Proximal Glomerular Tubule



In the proximal tubule, glucose, amino acid, phosphate, and sulfate are co-transported by the entry of sodium into the cells. On the other band, H + is counter-transported against sodium, leading to reabsorption of bicarbonate. Therefore, sodium transport in the proximal tubule, which accounts for 50 to 60% of the total Na + transport (accompanied by almost the same percentage reabsorption of filtered water), is mainly dedicated to solute and bicarbonate reabsorption that is linked to the largest proportion of Na + reuptake in the proximal tubular segment [5]. In normal physiology, SGLT2 and SGLT1 activity provides approximately 5% of Na + tubular reabsorption. In not compensated diabetic subjects SGLT2 and SGLT1 mRNA expression increase by 36% and 20%, respectively and, consequently, sodium glucose co-trasponders activity accounts for as much as 14% of total renal Na + reabsorption [3] thereby inducing a marked decrease in distal Na + delivery to the juxtaglomerular apparatus [6, 7].

The decreased Na + concentration in the filtrate is improperly sensed by the juxtaglomerular apparatus and perceived as a reduction in effective circulating plasma volume. This effect leads to local release of renin and angiotensin, resulting in prevalent constriction of the adjacent efferent arteriole, coupled with dilatation of the afferent arteriole secondary to local neuro-hormonal factors. The process leads to maladaptive glomerular afferent arteriole vasodilation provoking higher intraglomerular pressure. This mechanism is called tubule-glomerular feedback (TGF) [3, 8]. The net result of these intrarenal hemodynamic changes is an increase in GFR, defined as renal hyperfiltration when GFR trespasses the generally accepted threshold of ≥ 135 mL/min/1.73 m^2. Renal hyperfiltration is a marker of intraglomerular hypertension, a recognized risk factor for renal physiology derangement that triggers and runs progression of diabetic nephropathy [9, 10] as well as major renal damage in most cardiovascular conditions.

The pharmacological effects of sodium glucose cotransporters inhibition in diabetes

The administration of SGLT inhibitors (class of drugs named glifozines) generates effects that distinguish them from other anti-diabetes drugs. They promote glycosuria that leads to weight loss by dropping calories from the body to the urine and affects insulin resistance. On the other hand SGLT inhibitors avoid hypoglycemia by leaving metabolic counter-regulation intact [1]; they also reduce blood pressure consistently with their natriuretic effect and induce uric acid elimination as a result of inhibition of the tubular urate transporter URAT1. Last but not least, they reversibly lessen intraglomerular pressure and glomerular filtration rate (GFR) by activating the TGF [1, 3].

The pharmacological effect of florizine, a not specific SGLT2 and SGLT1 inhibitor, has been investigated in a diabetic and not diabetic animal model. The drug administration was followed by increased delivery of NaCl to distal renal tubule. The effect was present in diabetic and not diabetic animals, causing increased afferent arteriole tone, thereby decreasing intraglomerular pressure via TGF in both animals model and suppressing hyperfiltration in the diabetic animal. The investigation proved the impact of florizine in balancing Na + concentration sensed by the juxtaglomerular apparatus [9].

A similar effect has been achieved by the selective inhibition of SGLT2 in other animal models [11] and was elegantly proved in type1 diabetic patients [12].

It has to be highlighted the administration of selective and unselective SGLT inhibitors, in animals as well as in humans, is coupled with decreasing filtration rate impacting renal function as addressed by the eGFR decline.

In subjects with type 2 diabetes mellitus (T2DM), eGFR changes are characterized by acute, dose-dependent reductions of ≈ 5 mL/min/1.73 m^2. However, over several weeks after the initial drop, eGFR tends to return toward baseline and remains stable over time [3, 8].

The impact of SGLT2 inhibition on eGFR is also evident in patients with and without CKD and with and without HF, and is observed after 3 to 4 weeks treatment being, though, reversible within 2 weeks of drug discontinuation [3].

It has to be noted inhibitors of the RAAS also reduce intraglomerular pressure through efferent arteriolar vasodilatation, leading to drop of filtration rate with reduction in intraglomerular hypertension and renal hyperfiltration, resulting in nephroprotection [13]. According to eGFR change over time after treatment with RAAS blockade, patients with T2DM who were in the highest tertile of eGFR change within 3 months enjoyed the best renal function outcome [14].

Concordantly with mechanistic studies results, large clinical trials with cardiovascular endpoints in diabetics patients (CVOT) documented SGLT2 inhibitors to reduce cardiovascular events prominently related to heart failure (HF) exacerbation and to renal outcomes. Over the past few years, three seminal CVOTs investigating empagliflozin (EMPA-REG OUTCOME) [15], canagliflozin (the CANVAS Program) [16], and dapagliflozin (DECLARE TIMI-58) [17] reported their results. In a pooled analysis of these studies, SGLT2 inhibition conferred a 14% reduction in the incidence of major adverse cardiovascular (CV) events and a 24% reduction in the incidence of hospitalization for HF (HHF) compared to placebo [18] both in diabetics with atherosclerotic cardiovascular disease at baseline (secondary prevention) and with only cardiovascular risk factors (primary prevention). Notably, incidence of HHF was reduced in all three CVOTs, despite differences in baseline cardiovascular and renal risk (Fig. 2a). Moreover, SGLT2 inhibition reduced mortality in empaglifozin study performed exclusively in diabetics with cardiovascular diseases (Fig. 2a).

At baseline, approximately 80% of subjects investigated in the three CVOTs were taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). In this setting, SGLT2 inhibition substantially reduced albuminuria in patients across the spectrum of micro- and macroalbuminuria and, to a less extent, also the urine albumin to creatinine ratio.

The kidney in heart failure syndrome

It is important to remind intraglomerular hypertension is also a constituent of kidney pathophysiology in HF setting. Low cardiac output leads to under-filling of the arterial vasculature and blood flow is shunted from the kidneys to heart and brain circulation. This compensatory mechanism

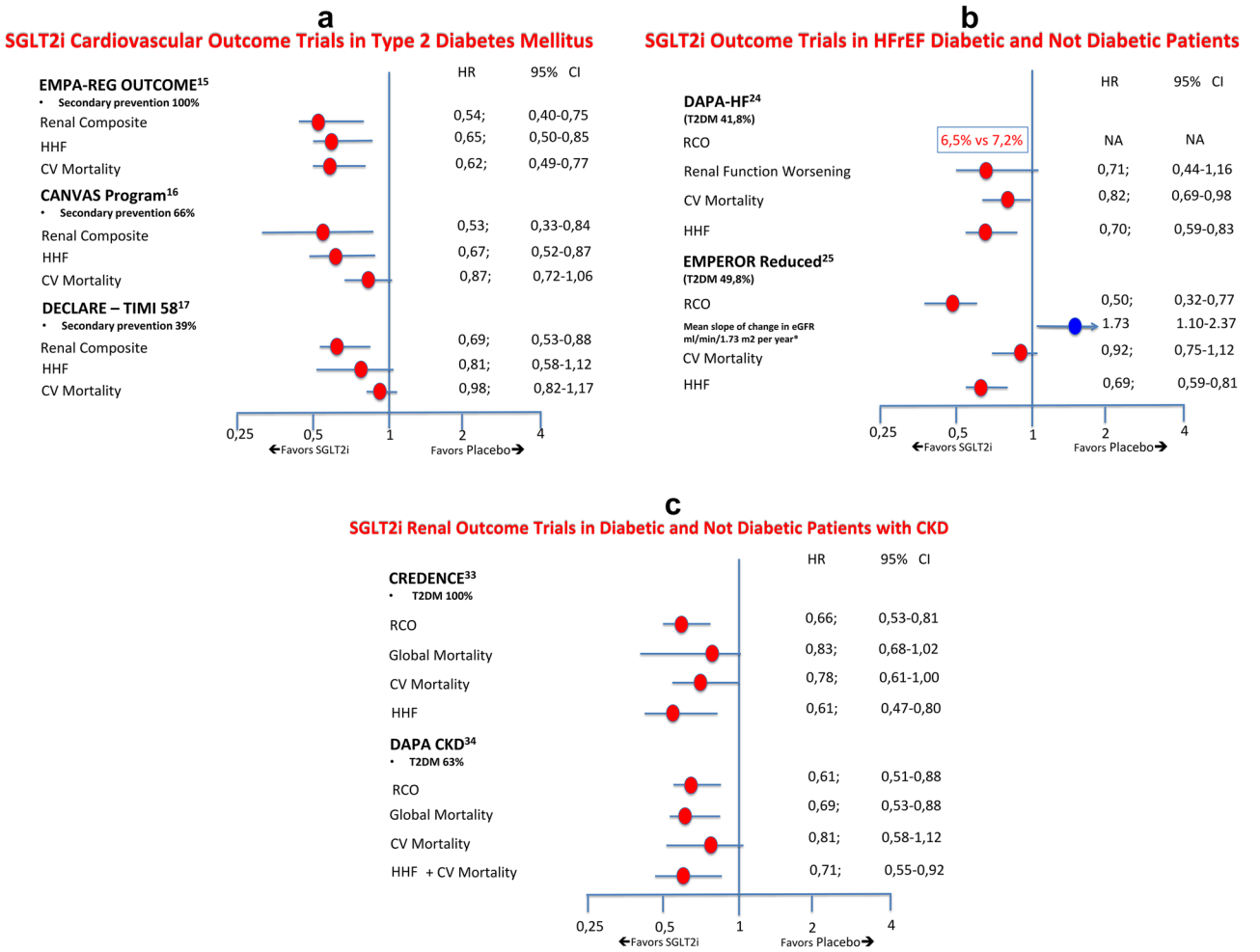


Fig. 2 Abbreviations and acronyms: RCO = renal composite outcome (doubling creatinine or kidney replacement therapy or cardiovascular-renal mortality). CV = cardiovascular mortality. HHF = hospitalization for heart failure. CVOT = cardiovascular outcome trial. T2DM = Type 2 diabetes mellitus. SGLT2i = sodium glucose cotransporter 2 inhibitors. HFrEF = heart failure with reduced ejection fraction. CKD = chronic kidney disease. **a** Three large CVOTs investigated SGLT2is effects in T2DM population with different CV risk as expressed by the proportion of subjects in secondary prevention ranging from 100 to 39%. Despite the disparity of disease severity, SGLT2i administration generated a rather homogenous HR reduction for CRO while HHF and CV mortality consistently declined in studies with the increasing proportion of patients enrolled for primary prevention. **b** Two large trials explored SGLT2i effects in HFrEF patients. The two investigated populations had different disease severity being more advanced with more severe kidney impairment in the EMPEROR Reduced in comparison to DAPA-HF that was based on larger population study design with relatively longer follow up (16 vs 19 months). The studies provide complimentary results. In both investigations, HHF decreased at the same extent, while CV mortality was affected with statistical significance only in DAPA HF, and CRO plus renal function worsening displayed statistically significant decrease only in EMPEROR Reduced trial. In EMPEROR Reduced "worsening of renal function" is indicated as "Mean slope of change in eGFR ml/min/1.73 m^2 per year" and is favored by placebo administration. **c** In studies conducted on patients with CKD with and without T2DM, characterized by low glomerular filtration (lower limit eGFR > 25 mL/min/1.73 m^2) with and without albuminuric nephropathy, the administration of canaglifozin (CREDENCE) and dapaglifozin (DAPA-HF) resulted in an early and unequivocal benefit on all the predefined envisaged outcomes, requiring the early closure of the two studies. On note the global mortality was decreased in almost statistically significantly fashion in CREDENCE while it was definitely significantly decreased in DAPA CKD

aims to preserve vitality of the two pivotal organs for the entire body survivability but entails disproportionate decrease of renal fraction of cardiac output [19].

One critical consequence of the greater imbalance in renal perfusion in HF patients is the consequent disproportionate enhancement of renal sympathetic efferent nerve activity that results in marked increases in renal and cardiac norepinephrine spillover and with a sympathetically mediated increase in plasma renin activity leading to higher angiotensin II (ATII) generation.

Angiotensin II plays pivotal role in kidney function by influencing the whole glomerular filtration rate, particularly affecting the glomerular plasma flow rate as it exerts potent vasoconstrictive action on afferent and efferent glomerular arterioles. The smaller section of the efferent vessel leads to a disproportioned increase of intraglomerular vascular resistances. The deleterious effect is amplified by ATII ability to contract and thereby to reduce glomerular capillary surface area and ultrafiltration coefficient, expression of the hydraulic glomerular conductivity [20].

In mild HF patients the sequel of ATII in renal physiology is the higher filtration pressure gradient between afferent and efferent arteriole exploited to increase the glomerular filtration fraction in order to preserve urine production [21]. As HF progresses the increased filtration fraction may not be adequate to compensate the low glomerular plasma flow in presence of the reduced hydraulic glomerular conductivity. The combination of these factors may not maintain the trans-capillary gradient higher enough [22] to preserve the renal compensatory function.

In these settings, the glomerular hyperfiltration deranges renal anatomy and physiology, as it is the prominent cause of glomerular basement membrane damage, glomerular endothelial dysfunction and extravasation of proteins into Bowman's capsule. Albumin loss in the urine is, indeed, an undisputable index of ominous HF outcome [23].

Selective and not selective SGLT inhibitors reduce intraglomerular pressure through restoration of afferent arteriole tone, with a modular action which accounts for better HF patient outcome based on nephroprotection in a clinical fashion that closely resembles what therapy with RAAS inhibitors achieves by vasodilating efferent arteriole. The two mechanisms of action are different, indeed, but works additively and consistently proved to ameliorate HF outcomes in two large study conducted in HFrEF populations receiving guideline directed medical therapy. In the dapaglifozin (DAPA HF) trial [24] the SGLT2 inhibition significantly decreased the incidence of the combined end point for CV mortality or HHF, and CV mortality alone was significantly decreased (Fig. 2b). In the empaglifozin study (EMPEROR Reduced) [25], the SGLT2 inhibition proved to be equally effective in decreasing the combined endpoint of CV mortality or HHF end, but the CV mortality decrease alone was not statistically significant. Interestingly only in the empaglifozin trial the renal outcomes were significantly affected in patients with HFrEF. The analysis of the studies design based on HFrEF populations with different risk profile indicated a more severe HF and more advanced CKD (stage II to IV) in the EMPEROR Reduced coupled with a shorter study follow-up, and this may account for the investigations' different results [24, 25]. On other hand, sotaglifozin, a not selective SGLT2-SGLT1 inhibitor, was investigated in unselected HF diabetics enrolled within acute decompensation (SOLOIST WHF) [26]. Despite the trial had anticipated termination due to SARSCov2 epidemic, the therapy proved highly effective in restraining soon the incidence of HHF, thus reinforcing the evidence SGLT inhibition is a highly effective therapy in preventing HF exacerbation. Impressively the benefit achieved by SGLT2 inhibitors in HFrEF phenotype was obtained on top of guideline directed medical therapy, embracing ACE inhibitors and ARBs. Such impressive result may synergistically connect afferent arteriole vasoconstriction due by SGLT2i action with efferent arteriolar vasodilatation induced by RAAS inhibitors. Both actions are effective in decreasing intraglomerular filtration pressure and result in nephron-protection, though at cost of GFR lowering. The action is consistent to eGFR change over time in patients with T2DM after treatment with RAAS blockade. Those who had the greatest tertile of eGFR change within 3 months enjoyed the best preservation of renal function [27].

Other data support the intraglomerular filtration pressure decline as leading mechanism affecting adverse cardiovascular outcomes in subjects receiving SGLT2is.

In the EMPEROR Reduced, empaglifozin administration was coupled by immediate GFR dip that subsequently tended to return toward baseline values, remaining stable overtime. At the opposite in the placebo arm, GFR was higher at the beginning, but than kept continuous slow declining, crossing the treated arm values on a longer term, addressing late significant loss of kidney function [25].

One more evidence supports the link between intraglomerular filtration pressure lowering and cardiovascular outcome improvement. In DAPA HF and in EMPEROR Reduced trials, SGLT2 inhibition on top to angiotensin renin neprelysin inhibitor (ARNI) therapy added further 25% and 23% decrease on primary endpoint [24, 25]. The benefit was achieved despite ARNI administration previously proved to be coupled with continuous GFR decline in the PARADIGM HF trial [28].

Chronic kidney disease, the unifying substrate for exploiting SGLT2 inhibition benefit

At present, chronic kidney disease (CKD) is generically defined by the threshold of estimated GFR uncorrected for the effects of aging, but it remains somewhat uncertain whether the age-related decline in renal function is associated with biological vascular damage or is due to chronological age per se. The combination of age-related vascular changes can provide the suitable substrate for the traditional cardiovascular risk factors to promote cardiovascular disease and CKD ensuing.

This point of view is supported by peculiar anatomy of the kidney based on a highly concentered and specialized vasculature that physiologically receives one fifth of stroke volume per heartbeat, namely the largest arterial blood volume delivered to a single body organ.

This high pressure, high volume flow entails continuous adjustment of intra-renal vascular resistances life along to assure stable function of kidney emunctorium, while renal vessels are simultaneously exposed to risk factors such as hypertension and wide pulse pressure, dyslipidemia, diabetes and smoking, accounting for intimal fibrosis, glomerulosclerosis, tubular atrophy, and interstitial fibrosis that are also aging histological features [29].

Clinical data suggested that age-related loss of renal function is more pronounced in older people in whom cardiovascular disease and risk factors coexist [30] specifically in those presenting microalbuminuria [31]

The combination of microalbuminuria and age-related vascular disease has consistently been shown to be associated with increased cardiovascular mortality. This was confirmed in a large cohort study where the sharpest increase in cardiovascular disease risk was noted in microalbuminuric subjects with GFR < 45 mL/min/1.73 m^2 [32]. Clinical data are consistent with the evidence that a considerable reduction in renal mass imposes increased workload of the remaining nephrons inducing hyperfiltration at the single nephron level leading to glomerular hypertrophy. The pathology is reflected in the histological findings characterized by global glomerulomegaly coupled with glomerulosclerosis in addition to segmental scars [33, 34]. However, it has to be reinforced that albuminuric kidney is prominently a consequence of glomerular hyperfiltration [32–34].

Table 1 Data in the table provide comparison of the studies population size analyzed in the manuscript, addressing the proportion of enrolled subjects with eGFR < 60 mL/min/1.73 m^2 on the basis of adopted eGFR calculation formula. The data emphasize the differences among investigated cohorts did not affect the reported outcomes concordance

Study Drug Journal Publication year	No. of enrolled patients eGFR % < 60 mL/min/1.73 m^2	eGFR calculation formula
EMPA-REG OUTCOME[15] (Empaglizozin) NEJM 2015	7020 26%	Modification of Diet in Renal Disease (MDRD) equation
CANVAS[16] (Canaglifozin) NEJM 2019	10,142 20.1%	Chronic Kidney Disease Epidemiology Collaboration formula
DECLARE TIMI 58[17] (Dapaglifozin) NEJM 2017	17,160 7%	Cockcroft and Gault formula MDRD equation Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI)
DAPA HF[24] (Dapaglifozin) NEJM 2019	4744 40%	CKD-EPI
EMPEROR Reduced[25] (Empaglizozin) NEJM 2020	3730 48%	CKD-EPI
CREDENCE[35] (Canaglifozin) NEJM 2019	4401 60%	CKD-EPI
DAPA CKD[36] (Dapaglifozin) NEJM 2020	4304 89%	CKD-EPI

The comprehensive picture provided by clinical and pathological data in CKD strongly highlights the decline of glomerular filtration pressure as the cornerstone of SGLT inhibitors benefit that was proved by two large, multicenter, randomized, double blind controlled trials performed in this population.

Both studies were stopped by recommendation of the independent data monitoring committee because of unquestionable efficacy of SGLT2 inhibition in diabetic and not diabetic subjects with CKD, with and without albuminuric kidney disease in decreasing adverse cardiovascular outcomes and in improving renal outcomes [35, 36] (Fig. 2c). On note, in both studies total mortality was affected by SGLT2 inhibition. The reduction was almost statistically significant in canaglifozin study and statistically significant in study performed with dapaglifozin (Fig. 2c).

Confirmatory results came from the controlled study which investigated sotaglifozin in 10,584 type 2 diabetics with eGFR between 25 and 60 mL/min/1.73 m^2. As previously addressed, this molecule simultaneously inhibits SGLT2 and SGLT1. The trial was discontinued after 16 months because SARS COV 2 outbreak and for this reason the research design was modified adopting the composite outcome of cardiovascular mortality, hospitalization, or urgent visit for heart failure as the primary outcome. In the short follow-up, the study reached the composite primary endpoint (HR 0.74; 95% CI: 0.63–0.88) and the secondary endpoint related to HF exacerbation only (HR 0.77; 95% CI: 0.66–0.91). The study results confirm early efficacy of SGLT inhibition in reducing the incidence of HF in CKD and strengthens the rapid benefit evidence generated by those molecules [37].

In order to highlight the consistency of SGLT2is in different clinical settings Table 1 provides additive data on studies analyzed in current paper. The data allow comparison of the population size of each study, addressing the proportion of enrolled subjects with eGFR < 60 mL/min/1.73 m^2 on the basis of adopted eGFR calculation formula. The data emphasize the differences among investigated cohorts did not affect the reported outcomes concordance.

Conclusions

The SGLT2 inhibitors, as a pharmacologic class, ushered uniform benefits in the composite outcome of renal adverse events as well as in the composite outcome of HF across different clinical settings spanning from diabetics in primary and secondary prevention to CKD patients with and without diabetes and with and without albuminuric kidney. Analogous improvement has been detected in HF patients with HFrEF, including patients with stage III CKD or in more advanced HFrEF and stage IV CKD and in diabetic HF patients within acute decompensated HF.

Equally compelling, however, is the observation that SGLT2i as class of drug maintain uniform benefit over HF and CKD outcomes across the different investigated clinical conditions as depicted in Fig. 2a–c.

The consistence of investigational data strengthens the hypothesis the effectiveness of those molecules is prominently generated by their action in the kidney. The point seems reinforced by the limited NT-proBNP change observed in the HF trials conducted with dapaglifozin (− 20%) [24] and with empaglifozin (− 5%) [25]. Although in treated arm of both studies the decline of plasma natriuretic peptide was statistically significant, the drop remained well below the meaningful threshold addressing clinical benefit [38].

It seems time to reshape our though putting heart, kidney and metabolism all together in the cardiovascular arena and support them by fighting their enemies all at once!

Declarations

Conflict of interest E.G. Gronda has no disclosure to declare. E. Vanoli has no disclosure to declare. M. Iacoviello was consultant for Astra Zeneca, Boehringer Ingelheim, Lilly, Merk Serono, Novartis, Vifor Pharma. S. Urbinati has no disclosure to declare. P. Caldarola has no disclosure to declare. F. Colivicchi has no disclosure to declare. D. Gabrielli has no disclosure to declare.

References

1. DeFronzo RA, Norton L, Abdul-Ghani M (2017) Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol 13(1):11–26. https://doi.org/10.1038/nrneph.2016.170
2. Gronda E, Iacoviello M, Caldarola P, Benvenuto M, Cassaniti L, Palazzuoli A, Municinò A, Napoli C, Gabrielli D (2021) Inibitori del co-trasportatore sodio-glucosio di tipo 2: meccanismi d'azione renale. Le implicazioni nel diabete e nello scompenso cardiaco [Sodium-glucose co-transporter 2 inhibitors: mechanisms of renal action. Implications for diabetes and heart failure]. G Ital Cardiol (Rome) 22(4):284–291. Italian. https://doi.org/10.1714/3574.35574. PMID: 33783448
3. Heerspink HJ, Perkins BA, Fitchett DH, Husain M, Cherney DZ (2016) Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 134(10):752–772. https://doi.org/10.1161/CIRCULATIONAHA.116.021887 (Epub 2016 Jul 28 PMID: 27470878)
4. Liu JJ, Lee T, DeFronzo RA (2012) Why do SGLT2 inhibitors inhibit only 30–50% of renal glucose reabsorption in humans? Diabetes 61(9):2199–2204. https://doi.org/10.2337/db12-0052.PMID:22923645;PMCID:PMC3425428
5. Matsubara M (2004) Renal sodium handling for body fluid maintenance and blood pressure regulation. Yakugaku Zasshi 124(6):301–309. https://doi.org/10.1248/yakushi.124.301 (PMID: 15170065)

6. Pollock CA, Lawrence JR, Field MJ (1991) Tubular sodium handling and tubuloglomerular feedback in experimental diabetes mellitus. Am J Physiol 260(6 pt 2):F946–F952
7. Vestri S, Okamoto MM, de Freitas HS, Aparecida Dos Santos R, Nunes MT, Morimatsu M, Heimann JC, Machado UF (2001) Changes in sodium or glucose filtration rate modulate expression of glucose transporters in renal proximal tubular cells of rat. J Membr Biol 182:105–112
8. Thomson SC, Vallon V (2019) Renal effects of sodium-glucose co-transporter inhibitors. Am J Cardiol 124 Suppl 1(Suppl 1):S28-S35. https://doi.org/10.1016/j.amjcard.2019.10.027. PMID: 31741437; PMCID: PMC7258222
9. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H (1999) Glomerular hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption. J Am Soc Nephrol 10(12):2569–2576. https://doi.org/10.1681/ASN.V10122569 (PMID: 10589696)
10. Ruggenenti P, Porrini EL, Gaspari F, Motterlini N, Cannata A, Carrara F, Cella C, Ferrari S, Stucchi N, Parvanova A, Iliev I, Dodesini AR, Trevisan R, Bossi A, Zaletel J, Remuzzi G (2012) GFR Study Investigators Glomerular hyperfiltration and renal disease progression in type 2 diabetes. Diabetes Care 35:2061–2068. https://doi.org/10.2337/dc11-2189
11. Thomson SC, Rieg T, Miracle C, Mansoury H, Whaley J, Vallon V, Singh P (2012) Acute and chronic effects of SGLT2 blockade on glomerular and tubular function in the early diabetic rat. Am J Physiol Regul Integr Comp Physiol 302:R75–R83. https://doi.org/10.1152/ajpregu.00357.2011
12. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC, von Eynatten M (2014) Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation 129(5):587–597. https://doi.org/10.1161/CIRCULATIONAHA.113.005081 (Epub 2013 Dec 13 PMID: 24334175)
13. Zatz R, Dunn BR, Meyer TW, Anderson S, Rennke HG, Brenner BM (1986) Prevention of diabetic glomerulopathy by pharmacological amelioration of glomerular capillary hypertension. J Clin Invest 77:1925–1930. https://doi.org/10.1172/JCI112521
14. Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, Parving HH, Brenner BM, Shahinfar S, Lambers Heerspink HJ (2011) An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int 80:282–287. https://doi.org/10.1038/ki.2011.79
15. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC (2015) Inzucchi SE EMPA-REG OUTCOME Investigators Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373(22):2117–28. https://doi.org/10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978
16. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR (2017) CANVAS Program Collaborative Group Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 377(7):644–657. https://doi.org/10.1056/NEJMoa1611925. Epub 2017 Jun 12. PMID: 28605608
17. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM (2019) Sabatine MS DECLARE–TIMI 58 Investigators Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 380(4):347–357. https://doi.org/10.1056/NEJMoa1812389. Epub 2018 Nov 10. PMID: 30415602
18. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS (2019) SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 393(10166):31–39. https://doi.org/10.1016/S0140-6736(18)32590-X. Epub 2018 Nov 10. Erratum in: Lancet. 2019 Jan 5;393(10166):30. PMID: 30424892
19. Shlipak MG, Massie BM (2004) The clinical challenge of cardiorenal syndrome. Circulation 110(12):1514–1517. https://doi.org/10.1161/01.CIR.0000143547.55093.17 (PMID: 15381655)
20. Pollak MR, Quaggin SE, Hoenig MP, Dworkin LD (2014) The glomerulus: the sphere of influence. Clin J Am Soc Nephrol 9(8):1461–9. https://doi.org/10.2215/CJN.09400913. Epub 2014 May 29. PMID: 24875196; PMCID: PMC4123398
21. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E (1997) Renal function in the elderly: impact of hypertension and cardiac function. Kidney Int 51(4):1196–1204. https://doi.org/10.1038/ki.1997.163 (PMID: 9083286)
22. Cody RJ, Ljungman S, Covit AB, Kubo SH, Sealey JE, Pondolfino K, Clark M, James G, Laragh JH (1988) Regulation of glomerular filtration rate in chronic congestive heart failure patients. Kidney Int 34(3):361–367. https://doi.org/10.1038/ki.1988.189 (PMID: 3172644)
23. Jackson CE, Solomon SD, Gerstein HC, Zetterstrand S, Olofsson B, Michelson EL, Granger CB, Swedberg K, Pfeffer MA, Yusuf S, McMurray JJ (2009) CHARM Investigators and Committees Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet 374(9689):543–50. https://doi.org/10.1016/S0140-6736(09)61378-7. PMID: 19683640
24. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde AM (2019) DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829
25. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F (2020) EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 383(15):1413–1424. https://doi.org/10.1056/NEJMoa2022190. Epub 2020 Aug 28. PMID: 32865377
26. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Voors AA, Metra M, Lund LH, Komajda M, Testani JM, Wilcox CS, Ponikowski P, Lopes RD, Verma S, Lapuerta P, Pitt B (2021) SOLOIST-WHF Trial Investigators. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med 14;384(2):117–128. https://doi.org/10.1056/NEJMoa2030183. Epub 2020 Nov 16. PMID: 33200892
27. Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, Parving HH, Brenner BM, Shahinfar S, Lambers, Heerspink HJ (2011) An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int 80:282–287. https://doi.org/10.1038/ki.2011.79
28. Packer M, Claggett B, Lefkowitz MP et al (2018) Effect of neprilysin inhibition on renal function in patients with type 2 diabetes

and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. Lancet Diabetes Endocrinol 6:547–554. https://doi.org/10.1016/S2213-8587(18)30100-1

29. Zhou XJ, Rakheja D, Yu X, Saxena R, Vaziri ND, Silva FG (2008) The aging kidney. Kidney Int 74(6):710–720. https://doi.org/10.1038/ki.2008.319 (Epub 2008 Jul 9 PMID: 18614996)
30. Baggio B, Budakovic A, Perissinotto E, Maggi S, Cantaro S, Enzi G, Grigoletto F (2005) ILSA Working Group. Atherosclerotic risk factors and renal function in the elderly: the role of hyperfibrinogenaemia and smoking. Results from the Italian Longitudinal Study on Ageing (ILSA). Nephrol Dial Transplant 20(1):114–23. https://doi.org/10.1093/ndt/gfh553. Epub 2004 Nov 30. PMID: 15572387
31. Brantsma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT (2005) PREVEND Study Group. Cardiovascular and renal outcome in subjects with K/DOQI stage 1–3 chronic kidney disease: the importance of urinary albumin excretion. Nephrol Dial Transplant 23(12):3851–8. https://doi.org/10.1093/ndt/gfn356. Epub 2008 Jul 18. PMID: 18641082
32. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351(13):1296–1305. https://doi.org/10.1056/NEJMoa041031.Erratum.In:NEnglJMed.2008;18(4):4 (PMID: 15385656)
33. Rennke HG, Klein PS (1989) Pathogenesis and significance of nonprimary focal and segmental glomerulosclerosis. Am J Kidney Dis 13(6):443–456. https://doi.org/10.1016/s0272-6386(89)80001-0 (PMID: 2658558)
34. Gupta K, Iskandar SS, Daeihagh P, Ratliff HL, Bleyer AJ (2008) Distribution of pathologic findings in individuals with nephrotic proteinuria according to serum albumin. Nephrol Dial Transplant 23(5):1595–1599. https://doi.org/10.1093/ndt/gfm833 (Epub 2007 Dec 8 PMID: 18065791)
35. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Trial Investigators CREDENCE et al (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. https://doi.org/10.1056/NEJMoa1811744
36. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC (2020) DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 383(15):1436–1446. https://doi.org/10.1056/NEJMoa2024816. Epub 2020 Sep 24. PMID: 32970396
37. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, Lewis JB, Riddle MC, Inzucchi SE, Kosiborod MN, Cherney DZI, Dwyer JP, Scirica BM, Bailey CJ, Díaz R, Ray KK, Udell JA, Lopes RD, Lapuerta P, Steg PG (2021) SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 384(2):129–139. https://doi.org/10.1056/NEJMoa2030186. Epub 2020 Nov 16. PMID: 33200891
38. Kim HN, Januzzi JL Jr (2011) Natriuretic peptide testing in heart failure. Circulation 123(18):2015–2019. https://doi.org/10.1161/CIRCULATIONAHA.110.979500 (PMID: 21555724)