Re-discover the value of protein binding assessments in hepatic and renal impairment studies and its contributions in drug labels and dose decisions

Jocelyn Courville[1] | Kathryn Roupe[2] | Gerhard Arold[3]

[1]Clinical Pharmacology—Drug Development Solution, ICON plc, Blue Bell, Pennsylvania, USA

[2]Clinical Pharmacology, Pharmacokinetics, Worldwide Clinical Trials, Austin, Texas, USA

[3]Clinical Pharmacology—Drug Development Solution, ICON plc, Langen, Germany

Correspondence
Jocelyn Courville, Clinical Pharmacology—Drug Development Solution, ICON plc, Blue Bell, PA, USA.
Email: jocelyn.courville@iconplc.com

Abstract

One of the key pharmacokinetic properties of most small molecule drugs is their ability to bind to serum proteins. Unbound or free drug is responsible for pharmacological activity while the balance between free and bound drug can impact drug distribution, elimination, and other safety parameters. In the hepatic impairment (HI) and renal impairment (RI) clinical studies, unbound drug concentration is often assessed; however, the relevance and impact of the protein binding (PB) results is largely limited. We analyzed published clinical safety and pharmacokinetic studies in subjects with HI or RI with PB assessment up to October 2022 and summarized the contribution of PB results on their label dose recommendations. Among drugs with HI publication, 32% (17/53) associated product labels include PB results in HI section. Of these, the majority (9/17, 53%) recommend dose adjustments consistent with observed PB change. Among drugs with RI publication, 27% (12/44) of associated product labels include PB results in RI section with the majority (7/12, 58%) recommending no dose adjustment, consistent with the reported absence of PB change. PB results were found to be consistent with a tailored dose recommendation in 53% and 58% of the approved labels for HI and RI section, respectively. We further discussed the interpretation challenges of PB results, explored treatment decision factors including total drug concentration, exposure–response relationships, and safety considerations in these case examples. Collectively, comprehending the alterations in free drug levels in HI and RI informs treatment decision through a risk-based approach.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Protein binding (PB) or unbound drug concentration is often evaluated in hepatic impairment (HI) and renal impairment (RI) clinical studies.

WHAT QUESTION DID THIS STUDY ADDRESS?

This review provide insights and case examples in the usage of PB results obtained in RI and HI studies in drug labels and highlights the contribution of PB to the overall understanding of PK, efficacy and safety.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Approximately 30% of approved label texts make reference to PB in HI and RI sections among drugs with PB data published in scientific journals. Changes in PB were found to align with a tailored dose recommendation in 53% and 58% of the approved label texts in HI and RI, respectively. The dose adjustment decision is complex, involving consideration of various key aspects.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This paper encourages clinicians, clinical pharmacologist, translational scientist, to acknowledge the complexity of drug and protein interaction and continue exploring their influences on clinical practice.

INTRODUCTION

The binding of a drug to plasma protein is a fundamental pharmacokinetic process that intricately connects free drug, total drug, the serum protein, and co-determines pharmacokinetics (PK) and pharmacodynamics (PD), and thereby efficacy and safety of the compound. Changes in the protein binding (PB) and the balance between total and unbound drug concentrations can be manifested in liver and renal disease, infection and inflammation, cancer, and other diseases.[1–3] Liver dysfunction and hepatic impairment may lead to reduced drug clearance and elimination by hepatic metabolism or biliary excretion, and they can also affect plasma PB due to reduced production of plasma proteins such as albumin and alpha-1-glycoprotein (AAG) as well as changes in their binding affinity or dynamics.[4–6]

Hepatic impairment based on Child–Pugh (CP) scores encompasses liver cirrhosis, even in the mild category. In patients with severe liver cirrhosis, the clearance of unbound midazolam was found to be only 14% of that in healthy controls, and the study revealed a highly significant correlation between individual CP score and unbound IV midazolam clearance.[7] The unbound clearance of midazolam decreased with increasing CP and model for end-stage liver disease (MELD) scores, and similar tread was observed for total midazolam clearance as well. Naproxen, characterized by high protein binding, has exhibited a significantly higher unbound fraction (f_u) in patients with chronic liver disease.[4,5] Typically, acidic and neutral drugs bind to albumin, and basic drugs bind to AAG.[3,8] AAG concentration (12–30 μM; 0.5–1.3 mg/mL) is much lower than albumin (35–50 mg/mL), and AAG displays only one binding site per molecule.[3,9] As a results, drug binding to AAG is saturable, fluctuations in AAG levels have the potential to substantially alter the free fraction of drugs that exhibits strong binding affinity to AAG.

Renal dysfunction, including renal impairment (RI), also result in changes in protein binding.[10,11] Patients with advanced liver cirrhosis often experience impaired renal function. The plasma binding of drugs, especially weak acids, may be significantly decreased in RI patients. This decreased binding is likely attributed to changes in protein concentration, changes in protein structure, and competitive displacers.[12] Protein bindings for diazepam, methotrexate, phenytoin, and theophylline are found to be decreased in renal diseases.[13] Phenytoin and valproic acid, both highly protein-bound drugs with narrow therapeutic window, require therapeutic drug monitoring for unbound drug level because their decreased binding in renal dysfunction.[7,10]

The FDA's hepatic impairment guidance suggests that for drugs highly extracted by the liver (extraction ratio >0.7) and extensively bound to plasma proteins (fraction unbound <10%, PB% ≥90%), determining f_u at least at trough and maximum plasma concentration is recommended. PK parameters such as clearance and volume should be appropriately expressed in terms of both unbound and total concentration of drug in plasm/serum/blood.[14] Additionally, drug clearance (unbound) and the effect of HI on PB of parent drug and metabolite (if applicable) maybe included in the drug label. EMA hepatic impairment guidance and other ICH guidance share similar principles, although these do not specify a specific f_u cutoff.[15] According to the FDA's renal impairment guidance, impaired renal function is associated with changes in plasma PB and/or tissue distribution of a drug.[16] The guidance indicates that for systemically active drugs and metabolites (if applicable), the unbound concentration generally determines the rate and extent of drug delivery to the sites of action. Determining f_u can be achieved using a few clinical samples or even a single sample from each patient, unless the binding is concentration-dependent or affected by metabolites or other time-varying factors, in which cases multiple samples may be necessary. The

degree of renal impairment maybe categorized based on parameters such as decreases in estimated creatinine clearance (CLcr) or changes in estimated glomerular filtration rate (eGFR). Additional analysis such as a population PK modeling maybe appropriate as well, when applicable. The unbound drug concentration whenever appropriate is recommended to use, for conducting population PK or exposure–response analyses.[16–18]

Most monoclonal antibodies are typically not required to be evaluated in HI or RI studies because they are subject to proteolytic catabolism and intracellular degradation after binding to their target without an expected major involvement of liver or kindey.[18,19] Nevertheless, in a recent review paper published by FDA colleagues,[20] dose adjustments were recommended in the label for 37% peptide drugs, all with molecular weight (MW) <69 kDa and 10% of drugs with protein structure in the context of renal impairment. Similarly, dose adjustments were recommended for hepatic impairment in the label for 35% of peptide drugs (all with MW <69 kDa) and for 5% of protein drugs.

Despite that PB concept is well-understood, there are limited concrete examples demonstrating the value and contribution of PB results obtained from these clinical studies. Therefore, we set forth to investigate case examples illustrating when and how these PB results were integrated into final prescribing labels conveying better treatment decisions. Additionally, we discussed and underscored the significance of understanding the interplay between total and free drug PK and PD as well as known exposure–response relationships, collectively, in making clinical meaningful decisions for drug posology in patients with hepatic and renal insufficiency.

METHODS

For this review, we utilized a PubMed/Medline systematic search combined with a Medical Subject Heading (MeSH) search ("protein binding" is a MeSH term) and then cross-checked with the Clinical trial.gov list of clinical trials of hepatic impairment or renal impairment with publications.

For hepatic impairment review

- PubMed keywords Query: allow oldest to be 1994 paper, mostly after year 2000, query up to Oct 2022 ((hepatic impair*) OR ("hepatic dysfunction") OR ("hepatic insufficiency") OR ("liver disease") OR ("impaired hepatic function") OR ("hepatic function") OR ("liver impairment")) AND (("clinical trial") OR ("Human trial") OR ("clinical study") OR

("human study")) AND ((pharmacokinetic*) OR (metabolism)) AND ((protein binding) OR ("free concentration") OR (unbound) OR (bound) OR ("unbound concentration"))
- MeSH term: "Liver Diseases/metabolism"[MeSH] AND "Protein Binding"[MeSH] + check "clinical trial" box
- Cross reference with clinicaltrials.gov on dedicated hepatic impairment studies and if a publication was available for that study, it was included in this review.

For renal impairment review

- PubMed keywords Query: allow oldest to be 1985 paper, mostly after year 2000, query up to Oct 2022 (("renal impair"*) OR ("renal dysfunction") OR ("renal insufficiency") OR ("kidney disease") OR ("impaired renal function") OR ("renal function") OR ("renal impairment")) AND (("clinical trial") OR ("Human trial") OR ("clinical study") OR ("human study")) AND ((pharmacokinetic*) OR (metabolism)) AND ((protein binding) OR ("free concentration") OR (unbound) OR (bound) OR ("unbound concentration"))
- MeSH term: Renal Insufficiency[MeSH] AND "Protein Binding"[MeSH] AND "metabolism" [MeSH], select only "clinical trial" box
- Cross reference with clinicaltrials.gov on dedicated renal impairment studies and if a publication was available for that study, it was included in this review.

After combining the results of all three search criteria and removing duplicate entries, a manual review was conducted to exclude review papers, non-drug-related studies and clinical studies that proved unrelated to hepatic or renal impairment.

For drugs with multiple commercial brands, we selected the product prescription label associated with the original publication. It is worth noting that product labels often have multiple versions, and for this review, we referred to the most recent version/year available on the "Drugs@FDA" platform. When a single compound had both discontinued and prescription versions, we used the prescription label, if accessible. In instances where a drug was approved both as a single agent and as part of a fixed combination, we prioritized reviewing the product label for the single agent whenever it was available.

RESULTS

Hepatic impairment

Based on the specified search criteira, a total of 67 HI publications were identified, all of which examined drug

protein binding in the clinical HI study. Additionally, we identified nine publications that combined HI and RI studies, and these were incorporated into both the HI and RI discussions. During our review of renal impairment data, we discovered five additional drugs lacking dedicated HI publications but had PB results referenced in the hepatic impairment section of their product labels. Consequently, these drugs were included in our discussion, resulting in a total of 72 drugs shown in Table S1.

Among the 72 drugs identified above, a total of 53 drugs have accessible prescribing information as FDA-approved label. Almost all product labels list the degree of protein binding (e.g., PB%) measured in *in intro* experiments under the Pharmacokinetics/Distribution section. Additionally, 17 of them (32%) include PB results or unbound drug concentration data in the Hepatic impairment or Special population sections of the label.

The selection of these 17 drugs with PB results incorporated into the label (Table 1) encompass a diverse range of drug classes and therapeutic areas, including oncology medicines, antibiotics, antivirals, immune modulators and drugs in neurology, treatment for hyponatremia, metabolic disease, insomnia, and hypertension. The majority of these drugs have a high degree of protein binding (i.e., PB% ≥90%), with exceptions being niraparib with 83% protein binding, palbociclib with 85% protein binding, linagliptin displaying concentration-dependent binding ranging from of 75% to 99%, and abrocitinib with 64% protein binding.

We proceeded to categorize and elaborate on these 17 drugs with four distinct groups:

1. *Dose adjustment for HI consistent with PB changes observed* (nine out of 17; 53%): In this category, the product label advises dose adjustment for HI, aligning with changes observed in PB results.
2. *No dose adjustment in HI despite some degree of PB changes* (one out of 17; 6%): Within this group, a single drug out of the 17 was described in the section below. Although some degree of change in PB was observed, the drug label does not recommend dose adjustment for HI.
3. *No dose adjustment, consistent with no PB change* (five out of 17; 29%): In this category, five out of 17 drugs fall under the umbrella where the product labels suggest no dose adjustment for patients with HI. This recommendation aligns with the absence of observed significant changes in PB.
4. *Dose adjustment, although there was no PB change* (two out of 17; 12%): Finally, among the 17 drugs, this group comprises two drugs. The drug labels indicate

dose adjustment in HI in absence of any noteworthy changes in PB.

Label recommends dose adjustment for HI with PB changed accordingly

Risperidone provides an illustration of adjusting the dosage in response to the observed rise in free drug concentration among patients with hepatic impairment, in the absence of significant changes in the overall PK of the total drug.[21] Risperidone binds to both albumin and AAG and has a narrow therapeutic window. The label states that an approximately 35% increase in the mean free fraction (f_u) in individuals with liver diseases was observed. The higher f_u of risperidone, due to diminished levels of both albumin and α1-acid glycoprotein in hepatic impaired patients, may result in an enhanced pharmacological effect. Therefore, a lower initial dose of 12.5 mg can be appropriate in patients with hepatic impairment, compared to approved regular dose of 25 mg (intramuscular injection) every 2 weeks.[22] The elevated f_u of the active moiety likely partially compensated for the reduced intrinsic clearance, resulting in a total apparent clearance in hepatic impaired subjects comparable to healthy subjects.

Selumetinib is a prescription medicine indicated for the treatment of children 2 years of age and older with neurofibromatosis type 1 (NF1) who have plexiform neurofibromas that cannot be completely removed by surgery. At the recommended 25 mg/m^2 twice-daily (BID) dose, it demonstrated a favorable benefit to risk profile, which maximizes clinical activity, while simultaneously minimizing the incidence and severity of adverse reactions. Selumetinib is a highly protein-bound drug (98.4%). In its HI study, clear correlations between increased unbound selumetinib exposure and increased CP score, decreased serum albumin, and increased prothrombin time were observed.[23] The unbound AUCinf increased by 41% in subjects with moderate HI, and increased 3.2-fold in subjects with severe HI, compared with normal subjects. The label recommends a 20% reduced dosage to 20 mg/m^2 BID for moderate HI and the recommended dosage for severe HI has not been established. The published FDA Clinical Pharmacology review document indicated that if multiple capsule strengths had been available, a 60% dose reduction to 10 mg/m^2 would be appropriate for severe HI.[24]

Conivaptan exhibits nonlinear PK and is highly protein bound with 99% binding over the wide concentration range of 10–1000 ng/mL. The approved dosing regimen consists of a loading dose 20 mg IV for 30 min followed by 20 mg/day for 2–4 days. The dosage maybe increased to 40 mg/day as necessary. The 80 mg/day dose was also explored,

TABLE 1 Reviewed FDA product labels that included protein binding results in the HI section.

Product name	Texts described in the product label related to PB	Dose recommendation for HI patients	Degree of PB
Risperidone	While the pharmacokinetics of risperidone in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by approximately 35% because of the diminished concentration of both albumin and α1-acid glycoprotein. Patients with impaired hepatic function may have increases in the free fraction of risperidone, possibly resulting in an enhanced effect	Risperidone doses should be reduced in patients with liver disease; Patients with renal or hepatic impairment should be carefully titrated on oral Risperidone before treatment with Risperidone is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with renal or hepatic impairment	90%
Lenvatinib	Protein binding of lenvatinib is 97% to 99%, which is independent of concentration and is not impacted by hepatic or renal function. Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable	Dose reduction is recommended for severe HI only	97%–99%
Siponimod	The unbound siponimod AUC parameters are 15% and 50% higher in subjects with moderate and severe hepatic impairment, respectively, in comparison with healthy subjects for the 0.25 mg single dose studied. The increased unbound siponimod AUC in subjects with moderate and severe hepatic impairment is not expected to be clinically significant. Protein binding of siponimod is greater than 99.9% in healthy subjects and in hepatic and renal impaired patients	No dose adjustments for siponimod are needed in patients with hepatic impairment	>99.9%
Selumetinib	Selumetinib unbound AUCinf decreased by 31% in subjects with mild hepatic impairment (Child–Pugh A), and increased by 41% in subjects with moderate hepatic impairment (Child–Pugh B), and 3.2-fold in subjects with severe hepatic impairment (Child–Pugh C) compared to subjects with normal hepatic function	Decrease the dose in patients with moderate impairment; dose for severe impairment was not established	98.40%
Conivaptan	The systemic exposure to unbound conivaptan doubled in subjects with moderate and severe hepatic impairment; In subjects with moderate and severe hepatic impairment, the area under the plasma concentration-time curve for unbound conivaptan was 2.3- to 2.5-fold the values observed in normal volunteers. The plasma protein binding of conivaptan decreased approximately 27% and 50%, respectively in patients with moderate and severe hepatic impairment	Decrease the dose in patients with moderate or severe hepatic impairment is recommended	99%
Ertugliflozin	Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment. The plasma protein binding of ertugliflozin was unaffected in patients with moderate hepatic impairment	No dose adjustment	93.60%

(Continues)

TABLE 1 (Continued)

Product name	Texts described in the product label related to PB	Dose recommendation for HI patients	Degree of PB
Zanubrutinib	The total AUC of zanubrutinib increased by 11% in subjects with mild hepatic impairment (Child–Pugh class A), by 21% in subjects with moderate hepatic impairment (Child–Pugh class B), and by 60% in subjects with severe hepatic impairment (Child–Pugh class C) relative to subjects with normal liver function. The unbound AUC of zanubrutinib increased by 23% in subjects with mild hepatic impairment (Child–Pugh class A), by 43% in subjects with moderate hepatic impairment (Child–Pugh class B) and by 194% in subjects with severe hepatic impairment (Child–Pugh class C) relative to subjects with normal liver function	The recommended dosage of zanubrutinib for patients with severe hepatic impairment is 80 mg orally twice daily, no dose adjustment needed for mild and moderate hepatic impairment	~94%
Lefamulin	Protein binding of lefamulin is reduced in subjects with hepatic impairment. Therefore, unbound (biologically active) lefamulin concentrations increased with the degree of hepatic impairment. On average, unbound lefamulin plasma AUC_{0-inf} was increased 3-fold in subjects with severe hepatic impairment compared to that in subjects with normal hepatic function	There is no information to evaluate the effect of hepatic impairment on the disposition of lefamulin following administration of Lefamulin Tablets. Lefamulin Tablets are not recommended in patients with moderate or severe hepatic impairment; for IV formulation, reduce the dosage of lefamulin injection to 150 mg infused over 60 min every 24 h in patients with severe hepatic impairment (Child–Pugh Class C)	94.8%–97.1%
Daridorexant	Label Figure 1: Effects of hepatic impairment and renal impairment on daridorexant PK. Hepatic impairment PK variables are based on the unbound fraction of daridorexant	The maximum recommended dosage in patients with moderate hepatic impairment (Child–Pugh score 7–9) is 25 mg of daridorexant no more than once per night; Daridorexant is not recommended in patients with severe hepatic impairment (Child–Pugh score ≥10)	99.70%
Niraparib	In a trial of patients with moderate hepatic impairment (total bilirubin ≥1.5 × ULN to 3.0 × ULN and any AST level) ($n=8$), niraparib AUC_{0-inf} was 1.56 (90% CI: 1.06 to 2.30) times higher compared with patients with normal hepatic function ($n=9$) following administration of a single 300 mg dose. Moderate hepatic impairment did not have an effect on niraparib C_{max} or on niraparib protein binding	Niraparib dosage reduction is recommended for patients with moderate hepatic impairment	83%
Linagliptin	Plasma protein binding of linagliptin is concentration dependent, decreasing from approximately 99% at 1 nmol/L to 75% to 89% at ≥30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment	No dose adjustment	75%–99% concentration dependent

TABLE 1 (Continued)

Product name	Texts described in the product label related to PB	Dose recommendation for HI patients	Degree of PB
Daclatasvir	The C_{max} and AUC(0-inf) of total daclatasvir (free and protein-bound drug) were lower by 46% and 43%, respectively, in Child–Pugh A subjects; by 45% and 38%, respectively, in Child–Pugh B subjects; and by 55% and 36%, respectively, in Child–Pugh C subjects. The C_{max} and AUC(0-inf) of unbound daclatasvir were lower by 43% and 40%, respectively, in Child–Pugh A subjects; by 14% and 2%, respectively, in Child–Pugh B subjects; and by 33% and 5%, respectively, in Child–Pugh C subjects	No dosage adjustment of daclatasvir is required for patients with mild (Child–Pugh A), moderate (Child–Pugh B), or severe (Child–Pugh C) hepatic impairment	99%
Brigatinib	Following a single dose of brigatinib 90 mg, unbound brigatinib systemic exposure (AUC_{0-inf}) was 37% higher in subjects with severe hepatic impairment (Child–Pugh C) compared to subjects with normal hepatic function. Unbound brigatinib systemic exposure (AUCinf) was similar between subjects with mild (Child–Pugh A) to moderate (Child–Pugh B) hepatic impairment and subjects with normal hepatic function	Reduce the dose of brigatinib for patients with severe hepatic impairment	91%
Tiagabine	In patients with moderate hepatic impairment (Child–Pugh Class B), clearance of unbound tiagabine was reduced by approximately 60%	Patients with impaired liver function may require reduced initial and maintenance doses of tiagabine and/or longer dosing intervals compared to patients with normal hepatic function	96%
Eprosartan	Eprosartan AUC (but not C_{max}) values increased, on average, by approximately 40% in men with decreased hepatic function compared to healthy men after a single 100 mg oral dose of eprosartan. The extent of eprosartan plasma protein binding was not influenced by hepatic dysfunction	No dosage adjustment is necessary for patients with hepatic impairment	~98%
Palbociclib	Binding of palbociclib to human plasma proteins in vitro was approximately 85%, with no concentration dependence over the concentration range of 500–5000 ng/mL. The mean fraction unbound (f_u) of palbociclib in human plasma in vivo increased incrementally with worsening hepatic function. Based on a pharmacokinetic trial in subjects with varying degrees of hepatic function, the palbociclib unbound exposure (unbound AUCinf) decreased by 17% in subjects with mild hepatic impairment (Child–Pugh class A), and increased by 34% and 77% in subjects with moderate (Child–Pugh class B) and severe (Child–Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function	No dose adjustment is required in patients with mild or moderate hepatic impairment (Child–Pugh classes A and B); For patients with severe hepatic impairment (Child–Pugh class C), the recommended dose of palbociclib is 75 mg once-daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days	85%

TABLE 1 (Continued)

Product name	Texts described in the product label related to PB	Dose recommendation for HI patients	Degree of PB
Abrocitinib	Dosage adjustment is not required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment based on similar combined unbound drug exposure (AUC$_{\mathrm{inf,u}}$) of abrocitinib and its two active metabolites, M1 and M2 compared to patients with normal hepatic function	Avoid use of abrocitinib in patients with severe (Child Pugh C) hepatic impairment. Dosage adjustment is not required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment	~64% (37% and 29% for M1, and M2 active metabolites)

Abbreviations: AUC$_{\mathrm{inf,u}}$, area under curve for unbound drug from 0 to infinity; f_{u}, fraction unbound; HI, hepatic Impairment; PB, protein binding; ULN, upper limit of normal.

but did not demonstrate a significant improvement over the 40 mg/day dose, and was associated with a higher incidence of infusion site reactions and a higher rate of discontinuations for adverse events (AE). In hepatically impaired patients, plasma PB decreased by approximately 27% and 50%, respectively, in patients with moderate and severe HI. Unbound drug AUC doubled (2.3- and 2.5-fold higher) in moderate and severe HI compared with the subjects with normal hepatic function.[25] Therefore, in patients with moderate (CP Class B) and severe (CP Class C) HI, the conivaptan label recommends a 50% lower loading of 10 mg over 30 min followed by an equally halved maintenance dose of 10 mg/day as a continuous infusion for 2–4 days. If serum sodium is not rising at the desired rate, conivaptan may be titrated upward to 20 mg/day.[26]

For zanubrutinib, an anticancer medication, the approved dose is 160 mg BID or 320 mg once-daily (QD). Unbound drug AUC increases were observed in various degree of hepatic impairment (i.e., increases of 23%, 43% and 194% for mild, moderate and servere HI, respectively). The total AUC also increased but with lower magnitude of changes, that is, by 11%, 21% and 60% in each of the category, respectively.[27,28] A correlation analysis between baseline albumin and f_{u} (at 2 h) confirmed that the increase in unbound exposure was greater than increase in total exposure, particular in severe HI. A 50% lower dose to 80 mg BID was recommended for severe HI since this reduced dose matched the unbound exposure in subjects with normal hepatic function. Given the smaller degree increase of PK exposure in mild and moderate HI for both total and unbound drug, and considering PK variability, a dose modification was not required for mild and moderate HI patients.[28]

The protein binding of lefamulin exhibited concentration dependence, with a higher mean f_{u} at the end of infusion compared to that at later times. The approved dose is 150 mg every 12 h for 5–7 days or 600 mg orally every 12 h for 5 days. E–R relationship was analyzed between free drug plasma AUC and minimal inhibitory concentration (MIC) and response; however, the distribution of total AUC was similar between responders and non-responders. This is likely due to the fact that most subjects already had

a high response rate, which limited the power to detect statistically a significant relationship. In hepatically impaired patients, decreased plasma PB was observed.[29] This resulted in higher unbound (biological active) lefamulin concentration and overall exposures. The unbound plasma AUC-inf of lefamulin increased threefold in subjects with severe HI compared to those with normal hepatic function. A population PK model was developed, accounting for nonlinear plasma PB and found that albumin level was one of the significant covariates. Consequently, the label advises a reduced lefamulin dose of 150 mg infused over 60 min every 24 h in patients with severe HI.[30]

In the case of daridorexant, the PK variables for HI patients presented in the label were based on the unbound concentration and were consistent with the clinical study finding in liver cirrhosis patients. Notably, the geometric mean of unbound AUCinf for the moderate and severe HI groups were 1.2- and 1.6-fold higher, respectively, than those in the normal group. The unbound $C_{\max}$ increased by 60% in moderate HI, and twofold increase in half-life was observed in moderate HI. For daridorexant, there is a positive dose–response relationship between dose level and various efficacy end points across dose range at 10–50 mg. The recommended dosage for daridorexant is 25–50 mg once per night. For moderate HI, the label recommends dose adjustment, permitting a lower dose with maximum recommended dosage of 25 mg not more than once per night. Dridorexant is not recommended in patients with severe HI.[31,32]

The approved dosage for brigatinib is 90 mg QD for the first 7 days, followed by an increase to 180 mg QD. Brigatinib's E–R analysis revealed a positive relationship between exposure and progression-free survival (PFS) and overall survival (OS). Exposure–safety relationships were also observed between predicted daily AUC and treatment-related Grade 3–4 AEs (e.g., increased creatinine phosphokinase, skin and subcutaneous tissue disorders, rash), and serious AEs (pneumonitis, pneumonia). Brigatinib safety and PK were investigated in varying degree of hepatic impairment. Unbound brigatinib exposure AUCinf was 37% higher in subjects with severe HI

compared with the healthy controls, and no change of exposure was found in mild and moderate HI. The label recommends a dose reduction by approximately 40% (i.e., from 180 to 120 mg, 120 to 90 mg, or from 90 to 60 mg) for patients with severe HI.[33]

Tiagabine is recommended as adjunctive therapy for the treatment of partial seizure in patients 12 years and older. In adults, tiagabine should be initiated at 4 mg once-daily, and the total daily dose maybe increased by 4–8 mg at weekly intervals until clinical response is achieved, to a maximum dose of 32–56 mg daily, in divided doses. The tiagabine label specifies a reduction of approximately 60% in the clearance of unbound tiagabine among patients with moderate hepatic impaired. Patients with impaired liver function may require reduced doses (including both initial and maintenance doses) or prolonged dosing intervals compared to those with normal hepatic function.[34]

The f_u of palbociclib in human was shown to increase incrementally with worsening hepatic function. The palbociclib unbound AUCinf increased by 34% and 77% in subjects with moderate and severe HI, respectively, compared to those in normal hepatic function. Similarly, unbound C_{max} of palbociclib increased by 7%, 38% and 72% for mild, moderate and severe HI, respectively. Due to limited data available at a fixed dose of 125 mg in patient studies, a definitive conclusion regarding an E–R relationship could not be made, but a greater reduction in absolute neutrophil count appears to be associated with increased palbociclib exposure. While patients with mild or moderate HI do not require dose adjustment, the label recommends a 40% reduced palbociclib dose (from 125 to 75 mg once-daily) for those with severe HI.[35]

Label indicates no dose adjustment in HI even though there are some degrees of PB changes

Siponimod treatment is initiated with a 5 day titration from 0.25 to 1.25 mg daily, followed by maintenance dose at 2 mg once-daily from Day 6. Dosage adjustment is required in patients with specific CYP2C9 genotypes. Siponimod is a highly protein bound drug with PB >99.9%. Unbound PK parameters (C_{max} and AUC) were unchanged in mild HI, but they were slightly increased by 15% and 50% in moderate and severe HI, respectively, compared with healthy subjects at the 0.25 mg single dose studied. The mean half-life of siponimod was unchanged in HI.[36] The increases observed for unbound AUC in moderate and severe HI, were not expected to be clinically significant. Close monitoring of patients with severe HI is required and treatment is to be discontinued if significant liver injury occurs.[37] The population PK analysis did not indicate significant impact from bilirubin, AST and ALT on its PK. The maintenance dose at 2 mg is believed at the near-maximal effectiveness and a higher dose of 10 mg was associated with a higher AE rates without benefit of improved efficacy.

Label indicates no dose adjustment, consistent with no PB change

Ertugliflozin's pharmacokinetics and safety were investigated in a dedicated reduced study design in moderately hepatic impaired group only. The AUCinf and C_{max} for unbound ertugliflozin were similar between moderate HI patients and healthy individuals. There was no change in estimated half-life either.[38] The mean f_u ranged from 0.034 to 0.041 in subjects with moderate HI and in patients with varying degree of renal impairment. As a result, there is no need for dosage adjustment in patients with mild or moderate HI. The use of ertugliflozin is not recommended for individuals with severe HI due to insufficient data.[39] The E–R relationship for sodium glucose co-transporter 2 (SGLT2) inhibitor ertugliflozin seems rather flat, with both 5 and 15 mg demonstrating comparable efficacy. The recommended dose remain as starting dose of 5 mg once-daily, increase dose to 15 mg daily in those tolerating ertugliflozin and needing additional glycemic control.

Antidiabetic agent linagliptin exhibits concentration-dependent protein binding with decreased binding observed at high drug concentrations. The 5 mg linagliptin once-daily is recommended per prescribing label. A dedicated multiple doses HI clinical study was conducted and found no changes in overall PK and safety after single and multiple doses of linagliptin in various degrees of hepatic impaired patients compared to those in healthy control.[40] In fact, the exposure was slightly lower in hepatically impaired patients than those of healthy. No dose adjustment is deemed necessary for HI population.[41]

For daclatasvir, a dedicated HI study investigated a 30 mg single oral dose in non-HCV hepatically impaired patients. The unbound exposure (C_{max} and AUCinf) was reported to be either similar or actually lowered in hepatically impaired subjects compared to those in the normal control group.[42] No discernable relationship was observed for daclatasvir-free fraction vs albumin concentration. No major differences were identified across daclatasvir exposure range when evaluating the exposure–efficacy relationship. In addition, daclatasvir exposure did not appear to play a major role in contributing to the reported AE of interest based on the E–R analysis. Therefore, the recommended dosage remains as 60 mg and no dosage adjustment is required for patients with mild, moderate, or severe HI.

ASCPT

The recommended starting dose for eprosartan is 600 mg QD when used as monotherapy (in patients who are not volume depleted). Eprosartan can be administered QD or BID with total daily dose up to 800 mg. The safety window is fairly wide, as eprosartan demonstrated good safety and tolerability at doses up to 1200 mg daily. Most AEs were of mild or moderate severity and did not require discontinuation. The prescribing information for eprosartan stated that eprosartan plasma PB was not influenced by hepatic dysfunction and no dosage adjustment is deemed necessary for patients with HI.[43] In fact, eprosartan total drug AUC (but not C_{max}) increased by approximately 40% with worsened hepatic function. Since eprosartan treatment maybe titrated to the described response, and given the totality of the data above, initial dose adjustment for HI is not considered necessary.

Abrocitinib is not a highly protein bound drug with PB at 64%. The prescribing dose for abrocitinib is 100 mg orally QD, allowing 200 mg for those not respond to 100 mg dose. Exposure–safety analysis indicated 100 mg QD is expected to provide a better safety coverage for a broader patient population. In the HI study, the concentration of combined exposure (AUCinf, u) of unbound parent drug and its two metabolites, representing the abrocitinib active moiety, remained similar between HI and healthy and the changes associated with liver function were not considered clinically meaningful.[44] Dose adjustment is unnecessary for mild and moderate HI based on similar PK of unbound abrocitinib ($AUC_{inf,u}$) and its two metabolites. Since abrocitinib was not evaluated in severe HI, the medication is not recommend for use in individuals with severe HI.[45]

Label indicates dose adjustment, but there is no PB change

Lenvatinib is a kinase inhibitor and is prescribed for patients with various types of cancer. The recommended daily dose ranges from 8 to 24 mg varying by indications. Serious hepatic adverse reaction and hepatotoxicity were observed across all clinical trials. The HI study observed no meaningful changes in overall PK in mild and moderate HI. The total drug AUCs increased 170% and half-life prolonged in subjects with severe HI. It is worth noting that further analysis showed the changes in total drug concentrations were smaller than those based on free concentrations, suggesting there were changes in plasma PB in subjects with severe HI, but it not considered clinical meaningful.[46,47] The label advises dose reduction for individuals with severe hepatic impairment. Monitoring liver function prior to initiating the treatment as well as throughout the treatment is recommended.

Niraparib exhibits concentration-independent binding to human plasma proteins with an average f_u of 0.17 at concentrations ranging from 1 to 50 μM. The label states that the metabolism of niraparib can potentially be altered by both genetic polymorphism in carboxylesterase as well as hepatic impairment. The recommended dose for patients weighing <77 kg or with a platelet count <150,000/μL, is 200 mg QD or otherwise dose is 300 mg QD. The prescribing label for niraparib advises a dosage reduction for patients with moderate HI. While moderate HI did not affect niraparib C_{max} nor PB, the total drug AUCinf increased to 1.56-fold in moderate HI when compared to normal control subjects.[48,49] For moderate HI, a reduced starting dose of niraparib to 200 mg once-daily is recommended, and patients are to be monitored for hematological toxicity.

Renal impairment

In accordance with the search criteria described above, a total of 58 publications were identified with studies relevant to this review. The 58 drugs are included in the Table S2. Out of the 58 drugs reviewed, 44 of them have available prescribing information as FDA-approved drug labels. Among these, a total of 12 product labels (constituting 27% of the total) have incorporated PB results within the context of the RI section. The majority of these 12 drugs have a high degree of protein binding (PB≥90%), except talazoparib with 74% protein binding, palbociclib with 85% protein binding and linagliptin with concentration-dependent binding ranging from 75% to 99% (Table 2).

The remaining 32 drug labels did not explicitly include information concerning PB in relation to the condition of renal impairment. This divergence highlights the variable extent to which PB is addressed within the context of renal impairment across different product labels.

We further categorized these 12 drugs with PB data in the context of RI into four distinct groups, each characterized as follows:

1. *Dose adjustment for RI consistent with PB changes observed* (one out of 12; 8.3%): This category applies to only one product label, with a dose adjustment in RI, that is consistent with PB change observed in RI patients.
2. *No dose adjustment, despite some degree of PB changes in RI* (three out of 12; 25%): Within this group, three product labels indicate no necessity for dose adjustment for the RI patients, despite of some degrees of PB changes in RI.
3. *No dose adjustment, consistent with no PB change in RI* (seven out of 12; 58.3%): In the majority of instances,

TABLE 2 Reviewed FDA product labels that included protein binding results in the RI section.

Product name	Texts described in the product label related to PB	Dose recommendation for RI patients	Degree of PB
Tiagabine	The pharmacokinetics of total and unbound tiagabine were similar in subjects with normal renal function (creatinine clearance >80 mL/min) and in subjects with mild (creatinine clearance 40 to 80 mL/min), moderate (creatinine clearance 20 to 39 mL/min), or severe (creatinine clearance 5 to 19 mL/min) renal impairment. The pharmacokinetics of total and unbound tiagabine were also unaffected in subjects with renal failure requiring hemodialysis	No dose adjustment	96%
Eprosartan	Following administration of 600 mg once-daily, there was a 70%–90% increase in AUC, and a 30%–50% increase in C_{max} in moderate or severe renal impairment. The unbound eprosartan fractions increased by 35% and 59% in patients with moderate and severe renal impairment, respectively	No initial dosing adjustment is generally necessary in patients with moderate or severe renal impairment, with maximum dose not exceeding 600 mg daily	~98%
Linagliptin	Plasma binding is not altered in patients with renal or hepatic impairment. Higher incidence of adverse reactions related to reduced renal function	Linagliptin is not recommended for use in patients with an eGFR less than 30 mL/min/1.73 m^2 and contraindicated in patients on dialysis	75%–99% concentration dependent
Daclatasvir	Using observed data, subjects with end-stage renal disease requiring hemodialysis had a 27% increase in daclatasvir AUC(0-inf) and a 20% increase in unbound AUC(0-inf) compared to subjects with normal renal function as defined using the Cockcroft-Gault CLcr formula. Daclatasvir is highly protein bound to plasma proteins and is unlikely to be removed by dialysis	No dosage adjustment of daclatasvir is required for patients with any degree of renal impairment	99%
Fingolimod	Fingolimod and fingolimod-phosphate are >99.7% protein bound. Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment. In adult patients with severe renal impairment, fingolimod C_{max} and AUC are increased by 32% and 43%, respectively, and fingolimod-phosphate C_{max} and AUC are increased by 25% and 14%, respectively, with no change in apparent elimination half-life	Based on these findings, the fingolimod 0.5 mg dose is appropriate for use in adult patients with renal impairment. Fingolimod 0.25 and 0.5 mg are appropriate for use in pediatric patients with renal impairment	>99.7%
Siponimod	Mean siponimod half-life and C_{max} (total and unbound) were comparable between subjects with severe renal impairment and healthy subjects. Unbound AUCs were only slightly increased (by 33%), compared to healthy subjects, and it is not expected to be clinically significant. The effects of end-stage renal disease or hemodialysis on the PK of siponimod has not been studied. Due to the high plasma protein binding (greater than 99.9%) of siponimod, hemodialysis is not expected to alter the total and unbound siponimod concentration	No dose adjustments are needed in patients with renal impairment	>99.9%
Ertugliflozin	Plasma protein binding of ertugliflozin is 93.6% and is independent of ertugliflozin plasma concentrations. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment	No dosage adjustment is needed in patients with eGFR ≥45 mL/min/1.73 m^2; Ertugliflozin is contraindicated in patients on dialysis	93.60%

(Continues)

TABLE 2 (Continued)

Product name	Texts described in the product label related to PB	Dose recommendation for RI patients	Degree of PB
Cabotegravir	As cabotegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis; No clinically significant differences in the pharmacokinetics of cabotegravir are expected with mild, moderate, or severe renal impairment. Cabotegravir has not been studied in patients with end-stage renal disease not on dialysis	No dose adjustment for renal impairment	>99.8%
Palbociclib	Binding of palbociclib to human plasma proteins in vitro was approximately 85%, with no concentration dependence over the concentration range of 500 to 5000 ng/mL. There was no obvious trend in the mean palbociclib f_u in human plasma in vivo with worsening renal function	No dose adjustment is required in patients with mild, moderate, or severe renal impairment (CLcr >15 mL/min). The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis	85%
Talazoparib	There was no evidence of a relationship between the protein binding of talazoparib and renal function	The recommended dose of talazoparib is 1 mg taken as a single oral daily dose, with or without food. For patients with moderate renal impairment (CLcr 30–59 mL/min), the recommended dose of talazoparib is 0.75 mg once-daily. For patients with severe renal impairment (CLcr 15–29 mL/min), the recommended dose of talazoparib is 0.5 mg once-daily	74%
Brigatinib	Following a single dose of Brigatinib 90 mg, unbound brigatinib systemic exposure (AUC_{0-inf}) was 86% higher in subjects with severe renal impairment [creatinine clearance (CLcr) 15 to 29 mL/min] compared to subjects with normal renal function. Based on a population pharmacokinetic analysis, brigatinib exposures were similar among 125 subjects with mild renal impairment (CLcr 60 to 89 mL/min), 34 subjects with moderate renal impairment (CLcr 30 to 59 mL/min) and 270 subjects with normal renal function (CLcr ≥90 mL/min)	Reduce the dose of brigatinib for patients with severe renal impairment	91%
Elbasvir and Grazoprevir	Elbasvir and grazoprevir are unlikely to be removed by peritoneal dialysis as both are highly protein bound. Overall, changes in exposure of elbasvir and grazoprevir in HCV-infected subjects with renal impairment with or without hemodialysis are not clinically relevant	No dose adjustment for subjects with renal impairment	>99.9% and 98.8%, respectively

Abbreviations: $AUC_{inf,u}$, area under curve for unbound drug from 0 to infinity; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; f_u, fraction unbound; PB, protein binding; RI, renal Impairment.

i.e., seven out of twelve labels, no dose adjustment is recommended in patients with RI, which is aligned with absence of any PB changes.

4. *Dose adjustment for RI although tthere was no PB change* (one out of 12, 8.3%): In this subset, a single drug label advises a dose adjustment for patients with RI, which is not connected with any alteration in PB.

Label suggests dose adjustment for RI with PB changed accordingly

Brigatinib is a kinase inhibitor indicated for anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer. In human ADME (absorption, distribution, metabolism, and excretion) study, 65% and 25% of the

administered dose was recovered in feces and urine, respectively. Unchanged drug accounted for 41% and 86% of the total radioactivity in feces and urine, respectively. The recommended dose is 90 mg QD for first 7 days and then increase to 180 mg QD. E–R analysis revealed that there is a dose–efficacy relationship, but relationship is relatively flat. The E–R relationship for safety indicates increase dose and exposure associated with increase safety risks. Population PK analysis has shown similar total drug exposures in patients with mild, moderate RI and subjects with normal renal function. The effect of severe RI on the pharmacokinetics of brigatinib was investigated in a dedicated clinical study as part of a commitment to a postmarking requirement (PMR).[50] An 86% increase in unbound brigatinib exposure (AUC_{0-inf}) was observed with severe RI when compared to those with normal renal function. Consequently, dose reduction by approximately 50% (i.e., from 180 to 90 mg, or from 90 to 60 mg) for brigatinib only for patients with severe RI is recommended.[33]

Label indicates no dose adjustment in RI even though there are some degrees of PB changes

The recommended dose for the antihypertensive eprosartan is 600 mg QD when used as monotherapy. Eprosartan exhibits moderate urinary excretion (i.e., 37% of the administered was drug recovered in the urine after IV administration in a radio-labeled ADME study). The medication can be administered once or twice daily with total daily dose from 400 to 800 mg. Based on a published RI study for eprosartan, f_u of eprosartan increased by 35% and 59% in patients with moderate and severe RI, respectively.[51] There was also a 70%–90% increase in total drug AUC and a 30%–50% increase in total C_{max} in moderate or severe RI. The label indicates that no initial dose adjustment is necessary in patients with moderate and severe RI providing that the maximum dose not to exceed 600 mg daily.[43]

The approved dose for daclatasvir is 60 mg QD in combination with sofosbuvir with or without ribavirin. Daclatasvir urinary excretion counts for less than 10% of the total drug. In human ADME study, 6.6% of the dose was excreted in the urine primarily as unchanged daclatasvir. Based on published FDA Clinical Pharmacology review document, no discernable relationship was observed for daclatasvir-free fraction vs albumin concentration. In addition, no major differences were identified across the daclatasvir exposure range in evaluating the E–R relationship for efficacy. The RI study reported that the geometric mean ratios for unbound drug AUCinf at CLcr 60, 30 and 15 mL/min were 1.18, 1.39 and 1.51, respectively, compared with normal renal function.[52]

These observed exposure increases in RI were considered within the range of variability and were not associated with an elevated risk of AEs. The label also states that subjects with ESRD requiring hemodialysis had a 27% increase in total AUCinf and a 20% increase in unbound AUCinf. Apparently in line with this modest increase of exposure, no dosage adjustment of daclatasvir is recommended for patients with any degree of RI per daclatasvir label.[42]

Siponimod is eliminated from the systemic circulation mainly due to metabolism, and subsequent biliary/fecal excretion. Unchanged siponimod was not detected in urine. The safety and pharmacokinetics of siponimod was evaluated in a dedicated renal impairment study with severe RI patients only.[53] The study revealed that while unbound C_{max} was comparable between severe RI patients and healthy controls, unbound AUC increased by 33% in RI and this increase was not considered clinically significant. A wide range of f_u between 0.0172% and 0.0550% was observed. Overall the mean half-life and C_{max} (for both total and unbound) were considered comparable between severe RI and healthy controls, and no dose adjustments are required for patients with RI.[37] The recommended dose for RI remains as label approved dose regimen which starts with treatment titration (starting 0.25 to 1.25 by Day 5), followed by maintenance dosage of 2 mg starting on Day 6.

Label indicates no dose adjustment, consistent with no PB change

For tiagabine, approximately 2% of an oral dose of tiagabine is excreted unchanged, with 25% and 63% of the remaining dose excreted into the urine and feces, respectively, primarily as metabolites. The overall PK remained similar in all subjects and no PK parameter (for both total or unbound concentrations) was found to be statistically correlated with estimated creatinine clearance.[54] No dose adjustment is required for use of tiagabine in RI. The product label states that subjects with renal failure requiring hemodialysis do not report any change of PK of total and unbound tiagabine either, underlining the tiagabine's PK stability across different renal conditions.[34] Tiagabine recommended dose is described in the previous HI section.

In patients with moderate RI, mean steady-state exposure of linagliptin increased compared with healthy subjects, that is, $AUC_{\tau,ss}$ by 71% and C_{max} by 46%. This increase was not associated with a prolonged accumulation half-life, terminal half-life, or any increased accumulation factor, and protein binding was unaffected either. Linagliptin exhibits low urinary excretion with approximately 85%

of the administered radioactivity after a single dose was eliminated via the enterohepatic system (80%) and urine (5%). No specific dose adjustment (remains as 5 mg QD) is recommended in the label for use in RI.[41–55] Since a higher incidence of AEs were observed with reduced renal function including in geriatric patients, linagliptin is not recommended for use in severe RI, defines as where eGFR<30 mL/min/1.73 m^2.

Fingolimod and fingolimod-phosphate are both highly protein-bound (>99.7%). Renal excretion seems to be a major route of elimination for fingolimod. After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. There is a clear relationship between exposure and response (all efficacy end points); however, the relationship is relatively flat without placebo within the observed exposure range. Fingolimod PB and fingolimod-phosphate PB are not altered in renal impairment. The total drug exposure was slightly increased in severe RI, that is, total C_{max} and AUC increased by 32% and 43%, respectively, while the elimination half-life remained unchanged.[56] These changes in observed PK were not considered clinically meaningful.[57] Based on these findings, the regular fingolimod 0.5 mg dose is considered appropriate for use in adult patients with RI. It is worth noting that substantial increases in two metabolites of fingolimod was observed in RI patients, but these were considered pharmacologically inactive metabolites, and the levels observed were covered by the preclinical safety range.

The starting dose for ertugliflozin is 5 mg QD, and an increase to 15 mg QD is allowed depending on individual response and tolerability. Ertugliflozin represents a moderate to high urinary excretion molecule with approximately 50.2% of the drug-related radioactivity eliminated in urine, after single dose based on human ADME study. In the RI study for ertugliflozin, no clinically meaningful differences in f_u of ertugliflozin were observed among the various renal function groups. In addition, the observed increase in total drug ertugliflozin exposure in subjects with RI was also not expected to be clinically meaningful.[58] No dosage adjustment is recommended in patients with eGFR ≥45 mL/min/1.73 m^2. Due to the potentially increased risk for volume depletion or hypotension, ertugliflozin is not recommended for use in patients with an eGFR less than 45 mL/min/1.73 m^2 and ertugliflozin is contraindicated in patients on dialysis.[39]

For cabotegravir, its product label indicates this is a highly protein-bound drug (>99%). The recommended dose for cabotegravir is 30 mg QD in combination with 25 mg rilpivirine orally. In human ADME study, approximately 27% of the drug was excreted in the urine as glucuronide metabolites. Cabotegravir's safety and pharmacokinetics was studied specifically in severely renal impaired patients (CLcr<30 mL/min) using a single oral dose of cabotegravir 30 mg.[59,60] The geometric mean ratio (90% CI) for unbound cabotegravir concentration was 1.31 and 1.51 at 2 h after dosing and 24 h after dosing, respectively. This difference was not considered clinically meaningful and severe RI was concluded not to impact total cabotegravir exposure. No dose adjustment is required in RI, but safety monitoring is recommended for severe RI patients.

The recommended doses for elbasvir (EBR) and grazoprevir (GZR) are 50 and 100 mg, respectively, once-daily in a fixed dose combination tablet for treatment of chronic HCV genotype 1 or 4 infections. The primary route of elimination of elbasvir and grazoprevir is through feces with almost all (>90%) of radiolabeled dose recovered in feces compared to less than 1% in urine. An E–R analyses showed that GZR exposure was not a significant predictor of response for sustained virologic response at posttreatment Week 12 (SVR12); however, EBR exposure was a significant predictor of SVR 12 at doses of 20 and 50 mg. The exposure–safety analyses showed that occurrence of late ALT/AST elevation was correlated with GZR exposures. GZR and EBR total drug AUCs were 65% and 86% higher, respectively, in non-HCV-infected subjects with severe renal impairment compared to matched healthy volunteers. No changes were identified in f_u in the severe RI.[61] In fact, f_u of grazoprevir was below quantification limit. GZR and EBR were minimally eliminated by 4-h hemodialysis. Overall, changes in exposure (total and free) of EBR and GZR in HCV-infected subjects with renal impairment with or without hemodialysis were not considered clinically relevant. Dose adjustment is not necessary for EBR and GZR in patients with any degree of RI, including patients receiving dialysis.[62]

Palbociclib exhibits an approximate protein binding of 85%, and this binding is not influenced by concentration. In human ADME study, 17.5% of the dose was recovered in urine and the majority of the material was excreted as metabolites. A definitive conclusion regarding an E–R relationship for efficacy was not made but a positive relationship seem to exist between exposure and safety, the latter being reduction in absolute neutrophil count for palbociclib. In a pharmacokinetic trial involving subjects with varying degrees of renal function, the total exposure (AUCinf) of palbociclib increased by 39%, 42%, and 31% in cases of mild, moderate, and severe RI, respectively. There was no discernible trend in the mean f_u of palbociclib in human plasma in vivo with worsening renal function.[35,63] The overall changes in total drug PK (AUCinf and C_{max}) were small and no dose adjustment is recommended in patients with mild, moderate, or severe RI, and with a CLcr of at least 15 mL/min. Palbociclib regular recommended dose is described in previous HI section.

Label suggests dose adjustment for RI without PB change

Protein binding of talazoparib is 74% in vitro, independent of talazoparib concentration. Renal excretion of talazoparib is the major route of elimination. Approximately 68.7% (54.6% unchanged) of the total administered radioactive dose was recovered in urine, and 19.7% (13.6% unchanged) was recovered in feces. The recommended dosing regimen is 1 mg QD allowing dose reduction in the event AE to the lowest dose of 0.25 mg QD. In RI patients, the steady-state drug total exposure (AUC_{0-24}) increased by 12%, 43%, and 163% in patients with mild (eGFR 60–89 mL/min/1.73 m^2), moderate (eGFR 30–59 mL/min/1.73 m^2), and severe (eGFR 15–29 mL/min/1.73 m^2) RI, respectively, relative to patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2). The steady-state peak concentration (C_{max}) increased by 11%, 32%, and 89% in patients with mild, moderate, and severe RI, respectively, relative to patients with normal renal function.[64,65] Drug plasma binding was measured on day 1 and day 22 of the study and no change was observed. Population PK analyses confirmed that moderate renal impairment and concomitant P-gp inhibitors increased total talazoparib exposure to the extent that necessitates talazoparib dose adjustment. Exposure-safety analysis indicated that higher exposure were associated with a higher risk for Grade ≥3 anemia and Grade ≥3 neutropenia. Collectively, dose reduction is recommended for individuals with moderate RI by 25% (from 1 to 0.75 mg) and severe RI by 50% (from 1 to 0.5 mg).

In patients with ESRD, hemodialysis is often used to help removing drugs from the body, but for highly protein-bound drugs (often with PB >99%), hemodialysis is less likely to be effective because only the unbound drug can be filtered.[10,66]

For the purpose of this review, drugs with product labels only mentioning PB in the dialysis section (i.e., not in the "Renal impairment" section), were not included in Table 2, but protein binding information undoubtedly contributes to comprehending the treatment decision. Examples of these drug labels are listed below (Table 3).

DISCUSSION

The present review addresses recently performed clinical studies in hepatic and renal impairment, with a specific focus on PB assessments, and how PB results contributed to label language and dose recommendations for these special populations. In the hepatic impairment review, the analysis of the product label revealed that the majority of the drugs (nine out of 17 labels, representing 53% of the cases) fell into the category of where the label suggested

TABLE 3 Examples of label texts regarding dialysis recommendation for highly protein-bound drugs.

Product name	Dialysis recommendation contributed from PB perspective	Degree of PB
Elvitegravir	As elvitegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by hemodialysis or peritoneal dialysis	99%
Daclatasvir	Daclatasvir is highly bound to plasma proteins and is unlikely to be removed by dialysis	99%
Cabotegravir	As cabotegravir is highly bound to plasma proteins (>99%), it is unlikely that it will be significantly removed by dialysis	>99.8%
Elbasvir and Grazoprevir	Elbasvir and grazoprevir are unlikely to be removed by peritoneal dialysis either, as both are highly protein bound	>99.9% and 98.8%, respectively
Lenvatinib	Due to the high plasma protein binding, lenvatinib is not expected to be dialyzable	97%–99%
Tiagabine	Since tiagabine is mostly metabolized by the liver and is highly protein bound, dialysis is unlikely to be beneficial	96%
Alectinib	Alectinib and its major active metabolite M4 are >99% bound to plasma proteins; therefore, hemodialysis is likely to be ineffective in the treatment of overdose	>99%
Daridorexant	Dialysis is unlikely to be effective, as daridorexant is highly protein bound	99.7%
Eprosartan	Eprosartan was poorly removed by hemodialysis	~98%
Siponimod	Due to the high plasma protein binding (greater than 99.9%) of siponimod, hemodialysis is not expected to alter the total and unbound siponimod concentration and no dose adjustments are anticipated based on these considerations	>99.9%
Linagliptin	Llinagliptin is not recommended for use in patients with an eGFR less than 30 mL/min/1.73 m^2 and contraindicated in patients on dialysis	Concentration dependent, up to 99%

Abbreviations: eGFR, estimated glomerular filtration rate; PB, protein binding.

a dose adjustment for HI, aligning with changes in PB accordingly. For renal impairment, the review indicated that the majority of the drugs (seven out of 12 labels, accounting for 58% of the cases) were categorized as "no dose adjustment, consistent with no PB change." Overall, the study findings emphasize the coherence between PB results and dose recommendation across both hepatic and renal impairment scenarios (Figure 1).
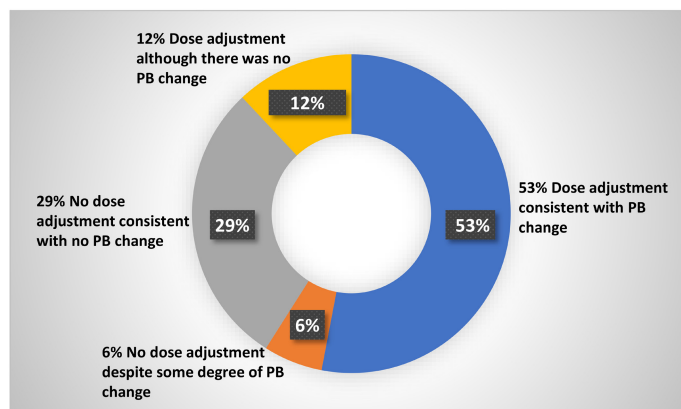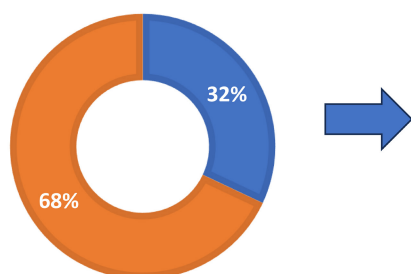
The scope of our reviewed studies is somewhat limited by the presence of "protein binding" related terms within dedicated renal and hepatic impairment studies. Therefore it is important to note that our list of studies is not exhaustive and does not encompass all relevant drugs in today's clinical practice. As examples, drugs such as naproxen and valproic acid were not included in our search, despite having pertinent PB data that contribute to dosage and treatment recommendation.[67,68] Further to this, it is noted that our review approached the subject matter from the scientific literature as a starting point, rather than the aggregate of label texts published since the last decades. Consequently, the total number of 121 drugs thus recovered from the scientific domain is a fraction of the total number of approved by the US FDA in recent decades (e.g. approximately 758 new drugs were approved from year 2000 to 2022).[69,70] This illustrates that a notable fraction of

past or recent clinical work in HI and RI, ideally including understanding the impact on PB, is not published or easily searchable from peer-reviewed scientific journals.

The challenges associated with measuring and interpreting of the PB data are multifaceted. We recognize that the treatment recommendation involves a collaborative decision-making process, considering factors such as total drug concentration, free drug concentration, the interplay of protein binding with other ADME properties, dose–response and concentration-response relationships for safety and efficacy, and other pertinent aspects. Upon closer examination of each category in HI and RI, we have identified a couple of key areas for discussion that can be gleaned from this comprehensive review.

First, the significance of the unbound drugs level should be emphasized. The binding of a drug to plasma proteins is frequently the initial stage in its distribution, action, and elimination. Human albumin serves as the primary carrier for drugs in adult humans. The binding of drugs to plasma proteins, including albumin and AAG, is typically reversible, occurs at specific sites, and is a major determinants in drug disposition. Given that protein-bound drugs can not readily leave the capillaries, only the free fractions can be distributed to tissues, thereby exerting pharmacological activity.[6,66] Impaired liver and kidney function results in
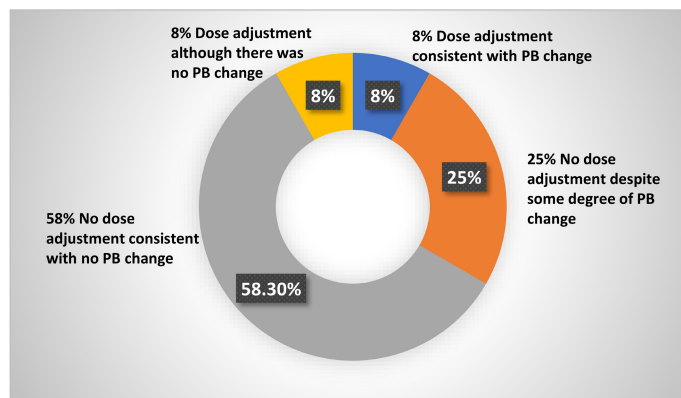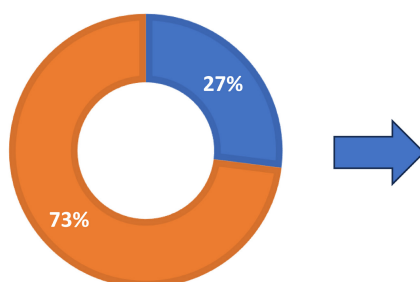
FIGURE 1 Percentage of FDA product label included PB information in HI and RI sections (among drugs studied PB and published in scientific journals) along with percentage of dose adjustment with or without PB change.

reduced plasma protein binding of drugs and this changes the availability of the circulating drug pool for tissue uptake and PK and PD. Traditionally, the protein binding aspect is often considered important for anti-bacterial, anti-viral and anti-convulsant medications.[6,66,71–73] Penetration into the extravascular space is highly important for anti-microbial therapy, as the majority of bacterial and fungal infections occur in the interstitial fluid of tissue.[72] The efficacy of flucloxacillin, for example, is dependent on the unbound concentration above the MIC.[74,75] For antibacterials with efficacy driven by unbound C_{max}, higher dosing, rather than more frequent dosing, would be appropriate. The pharmacological activity of anti-viral drugs for HIV is dependent on unbound drug entering cells that harbor the human immunodeficiency virus.[76] Applying the same principle, treatment paradigms across various therapeutic areas now consider unbound drug levels when determining appropriate dose levels for individuals with HI or RI. This is reflected by our review with 27%–32% of the RI and HI sections of the prescribing labels incorporating specific PB results. The majority of these labels indicate dose adjustment decisions for HI and RI that are consistent with PB findings.

Second, it is essential to understand how the interplay among protein binding, free drug concentration, total drug concentration, and other crucial parameters collectively inform optimal dose decisions. When free drug and total drug level change in the same direction, the fraction unbound may remain constant and the total drug exposure level is used for making dose decision. Reflected in our review, for the category of "dose adjustment even though there is no PB change," total drug exposure change might likely have been be the decisive factor. However, Deitchman, et al, described the recent development of tetracycline derivatives, and revealed atypical nonlinear protein binding with decreasing unbound fraction with increasing total concentration. Such drug displays linear PK in the free form, but nonlinear PK for the total drug.[77] On the other hand, the label for valproate acid emphasizes that monitoring of total concentrations could be misleading since free concentrations maybe be substantially elevated in patients with hepatic diseases whereas the total concentrations may appear to be normal.[68,78] The impact of plasma protein binding extends beyond distribution, influencing processes like drug metabolism and elimination. Notably, both hepatic uptake and glomerular filtration exhibit a direct proportionality to the free drug fraction present in the plasma. Utilizing drug clearance calculation, in the "well-stirred" or "venous equilibration" model, hepatic drug elimination is determined by blood flow, drug binding or free fraction and intrinsic clearance. The details about relationship between PB, extraction ratio, intrinsic clearance, volume of distribution, half-life

have been previously discussed.[8,71,72,79–81] Reduced plasma protein binding can lead to an increase in the total plasma clearance, but this should be not misinterpreted as an increased capacity of the patient to eliminate the drug.[4] Based on the draft RI guidance published in 2020 by FDA, "dosage recommendations in patients with impaired renal function should be determined based on overall understanding of the relationship between renal function, drug exposure, and the exposure-response relationship. These dosage recommendations may be based on exposure matching to a reference group." While exposure matching or exposure–response matching may appear straightforward in concept, its implementation can be challenging. In addition, it is not clear if additional approaches exists that can effectively differentiate the need for dose adjustment among mild, moderate and severe RI separately. The determination of the reference can also be ambiguous since the goal is to balance between safety and efficacy for each category and the difficulty in establishing a clear "no-effect" boundary.[16,82] Protein binding data nevertheless contribute to the exposure measurements and other ADME characterization. We summarized key considerations for deciding when to monitor the free drug concentration and factors to take into account when making dose modification decisions in Table 4.

Third, the extent to which alterations in protein binding or other significant parameters HI and RI are deemed clinically meaningful raises a crucial question. Reflected in the category of "dose adjustment with PB change accordingly." Any increase of unbound exposure (AUC or C_{max}) is to be interpreted in the setting of expected interindividual variability. Therefore when any of the key PK parameters deviates by a twofold difference from the control group, triggering considerations on the need of a dose modification is common. In some cases, an unbound exposure increase exceeding 50% compared to the control can already be deemed clinically relevant and the decisions factors (e.g., therapeutic window and E–R relationship) often are tightly linked to safety prediction. For the drugs in the category of "dose adjustment with or without change in PB" in our review, particular dose change only for severe group of HI and RI, highlights that these decisions often prioritize safety consideration. Outside our view, the literature also suggests that patients with liver cirrhosis may be more sensitive to the central adverse effects of opioids and the renal adverse effects of NSAIDs, partially linked to the increased unbound drug concentration.[4,83] Anti-depressants are mostly highly protein bound, the altered pharmacodynamics effects and increased safety risk in severe HI necessities a lower than usual titration and careful monitoring for steady state accumulation.[84] For nilotinib, while the hepatic study indicated no need for

TABLE 4 When to monitor the free drug concentration and important factors to consider when making dose adjustment or treatment decisions.

When to monitor total drug at a minimal	When to additionally monitor free concentration (and unbound fraction)	Important factors to consider when making dose adjustment or treatment decisions
Product Characteristics • Not a high protein binding drug (e.g. <90%) • Primary cleared by liver and kidney (e.g., small molecules, peptides); extensively metabolized by liver enzyme • Drugs with moderate or low hepatic extraction ratio (Eh) between 0.3 and 0.7 or lower than 0.3 *Total and Free drug relationship* • Total drug and free drug changes in the same direction and in similar magnitude *Bioanalytical assay limitation* • With no highly sensitive, reproducible protein binding assay support	*Product Characteristics* • Highly protein bound (e.g. ≥90%) • Narrow therapeutic window drug with low fraction of unbound (f_u) or the therapeutic dose level is already close to the toxicity level • Drugs with small volume of distribution and long half-life *Total and Free drug relationship* • The binding process is saturable or nonlinear or concentration dependent • Unknown whether total drug and free drug would change in the same direction *Patients characteristics* • Plasma protein level is expected to change (albumin, AAG) in particular disease setting (e.g. hepatic/renal impairment, cancer, heart disease, inflammation) • Possible concomitant use of other drugs with high PB • Accumulation of endogenous compounds (e.g., hyperbilirubinemia) that affect PB	*PB, PK change* • Total drug or unbound drug exposure (AUC, C_{max}) increased above the level of inter-individual variability (e.g. increase by >50%) • Factor other active moiety (ie active metabolite) into the decision making • When intrinsic metabolism reduced in patients even without PB change *Treatment types* • Dose is fixed (i.e. not titrated to response) • Balance between fixed dose adjustment vs clinical monitoring (for safety and PK) in real time • For highly protein bound drug (PB > 99%), hemodialysis is less likely to be effective for ESRD patients *Exposure-response relationship* • Existing exposure-safety relationship; in the case of significant rise in unbound (or total) drug concentration, increased AE rate or severity might be expected • Different dose adjustment methods maybe used based on the severity of organ impairment; prioritizing safety in the severely impaired HI and RI patients might be more appropriate than extrapolating from exposure-response curve of a reference *Specific safety concern* • Drugs possibly induce hepatotoxicity/ liver injury/kidney injury- relevant particularly for severe HI and RI • Drugs may pose safety risk to CNS system or cardiovascular system

Abbreviations: AAG, α1-acid glycoprotein; AUC, area under curve; CNS, central nervous system; Eh, hepatic extraction ratio; ESRD, end-stage renal disease; f_u, fraction unbound; HI, hepatic impairment; PB, protein binding; PK, pharmacokinetics; RI, renal impairment.

any dose adjustment, the label recommends reducing starting dose for subjects with HI due to possible hepatotoxicity.[85,86] For severely impaired HI or RI patients, prioritizing safety may become more important than the exposure matching for efficacy. This is because exposure-safety curves observed in healthy subjects or in mild and moderate categories may not accurately reflect the severe HI or RI population. Moreover, many late phase efficacy studies may have excluded the severely organ impaired patients. In such cases, a dedicated HI and RI or modeling and simulation approaches are conducted to supplement the knowledge gap. Reduced study design representing a worst-case scenario maybe selected,

where only severely impaired patients have been studied (e.g. siponimod, brigatinib RI studies). All of these factors additionally creates complexity of establishing a uniform dose adjustment strategy across different categories of organ-impaired groups.

There is a general consensus on three main evaluation criteria to decide when PB of a drug change would lead to clinical consequences.[71] These criteria include drugs that are highly protein-bound, drugs with high clearance and drugs for which dosing is not titration based on the desired effect. For the medicines using dose titration method to achieve a target response or target concentration, a fixed dose adjustment method might not be

necessary. Therapeutic drug monitoring based on unbound concentration offer more therapeutic advantages even when the unbound concentration cannot be accurately estimated from the total concentration.[74,75] This is reflected in our case examples within the categories of "no dose adjustment even though there was some degree of PB change" or "no dose adjustment consistently with no PB change," where most therapies are administered in titration fashion. In the case of conivaptan, dose titration is also allowed at later time after the initial dose reduction in HI patients, in case of a poor drug response.[25]

In summary, this paper delves into protein binding as a crucial ADME property for most small molecule drugs, influencing pharmacological activity, and potentially impacted by hepatic and renal dysfunction. We examined case examples where protein binding results are integrated in the drug prescription label, and contribute, to treatment optimization. Dosage adjustment, when necessary in patients with HI and RI, avoid excessive accumulation of the drug and of any active metabolites, mitigates risk of serious and/or severe adverse reactions and maintains treatment efficacy. While these case examples provide insights into decision-making factors, the limited amount of data does not allow defining unambiguous correlation between protein binding and dose adjustment in a generalized manner. Instead, a risk-based approach is deemed most suitable for making adjustments to optimize treatment and guiding clinical practice. Considering findings from various studies, such as human mass balance, determination of renal excretion, *in intro* and in vivo determination of metabolism and active metabolites, absorption and bioavailability, and drug–drug interactions, E–R relationships, provides a rationale and alternative approach to thoroughly assess the impact of hepatic and renal function on drug PK and safety. This, in turn, validates the selection of appropriate doses for patients with RI or HI. Furthermore, since the extent of the drug binding may be influenced by acid–base properties and specific solubility characteristics of active pharmaceutical ingredients, there is a need for potential research expansion of research to include these factors. This would further enhance the refinement of studies concerning the extent of plasma protein binding and its implications for dose adjustment in patients with renal or hepatic impairment.

AUTHOR CONTRIBUTIONS

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ORCID
Jocelyn Courville https://orcid.org/0000-0002-5512-1016
Gerhard Arold https://orcid.org/0009-0008-2449-622X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.