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REVIEW ARTICLE

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The short-term effect of hemodialysis on the level of high-sensitive cardiac troponin T — A systematic review

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Abstract

Introduction: Patients with end-stage renal disease (ESRD) have an increased risk of cardiovascular disease, but interpreting cardiac troponin is difficult in this population. The effect of renal replacement therapy (RRT) is important to consider when interpreting serial cardiac troponin T (cTnT) results for patients with ESRD suspected of acute coronary syndrome (ACS). The aim of this systematic review is to answer how low-flux hemodialysis (LF-HD), high-flux hemodialysis (HF-HD), and hemodiafiltration (HDF) affect the blood concentration of high-sensitive cardiac troponin T (hs-cTnT).

Method: Several databases were searched and identified records were evaluated independently by two of the authors. Pre- and postdialysis hs-cTnT concentrations together with other relevant data were extracted from the included studies. The quality (potential bias and applicability issues) were assessed for each of the included studies.

Results: The literature search identified 2,540 records and 15 studies were included. The relative pre- to postdialysis change of hs-cTnT varied from −41 to 29%. LF-HD increased the hs-cTnT concentration with relative changes between 2 and 17%. HDF decreased the concentration with relative changes from −41% to −9%. Both increases and decreases were seen for HF-HD (−16% to 12%).

Discussion/Conclusion: In this systematic review, we found LF-HD to increase the hs-cTnT concentration and HDF to decrease the concentration. Results for HF-HD and unspecified HD are more heterogeneous. Because of the differences between the included studies, a meta-analysis was not meaningful. This systematic review can help with the assessment of patients with ESRD suspected of ACS in relation to hemodialysis/HDF treatment.

1 | INTRODUCTION

Patients with end-stage renal disease (ESRD) have an increased risk of cardiovascular disease with odds ratios ranging from 20 to 1,000.[1] However, interpreting cardiac troponin levels is difficult in this population, as most patients with ESRD have a baseline level above the 99th percentile. Additionally, heart ischemia may present with atypical symptoms or even silent ischemia in these patients.[2]

Cardiac troponin T (cTnT) and I are expressed almost exclusively in the heart, where they are components of the contractile apparatus. Cardiac troponin measurements are essential to diagnose acute myocardial infarction (AMI). The biochemical aspect of the diagnosis requires a rise and/or fall of cardiac troponin with at least one value above the 99th percentile. For patients with an initial value above the 99th percentile, an expert group has recommended that serial changes >20% are significant.[3]

Several studies have investigated the effect of renal replacement therapy (RRT) on the concentration of cTnT, but increases,[4] decreases,[5] and virtually no change[6] have all been observed. However, there are differences to the RRT between the studies. Both hemodialysis (HD) with low-flux membranes (LF-HD),[4] HD with high-flux membranes (HF-HD),[5] and hemodiafiltration (HDF)[7] have been used.

These differences matter to the clearance of molecules. High-flux membranes have a poor clearance of molecules >15 kDa, while HDF increases the clearance of molecules up to ≈25 kDa.[8] Intact cTnT has a molecular weight of 40 kDa, but smaller cTnT fragments can be found in blood from patients with AMI,[9] and one study reported that only cTnT fragments <18 kDa are present in blood from patients with ESRD.[10]

The effect of HD/HDF is important to consider when interpreting serial cTnT results for patients with ESRD suspected of acute coronary syndrome (ACS) in relation to HD/HDF treatment. To the best of our knowledge, no systematic review addressing this exists.

High-sensitive cardiac troponin assays were introduced in 2010. These assays can measure cardiac troponin at much lower levels than older generation assays.[11]

The aim of this systematic review was to answer how LF-HD, HF-HD, and HDF affect the blood concentration of high-sensitive cTnT (hs-cTnT).

2 | METHOD

To conduct this systematic review, we identified studies investigating the short-term effect of HD or HDF on the blood concentration of hs-cTnT. Short-term here refers to studies that measure hs-cTnT before dialysis (predialysis) and after dialysis (postdialysis). Studies had

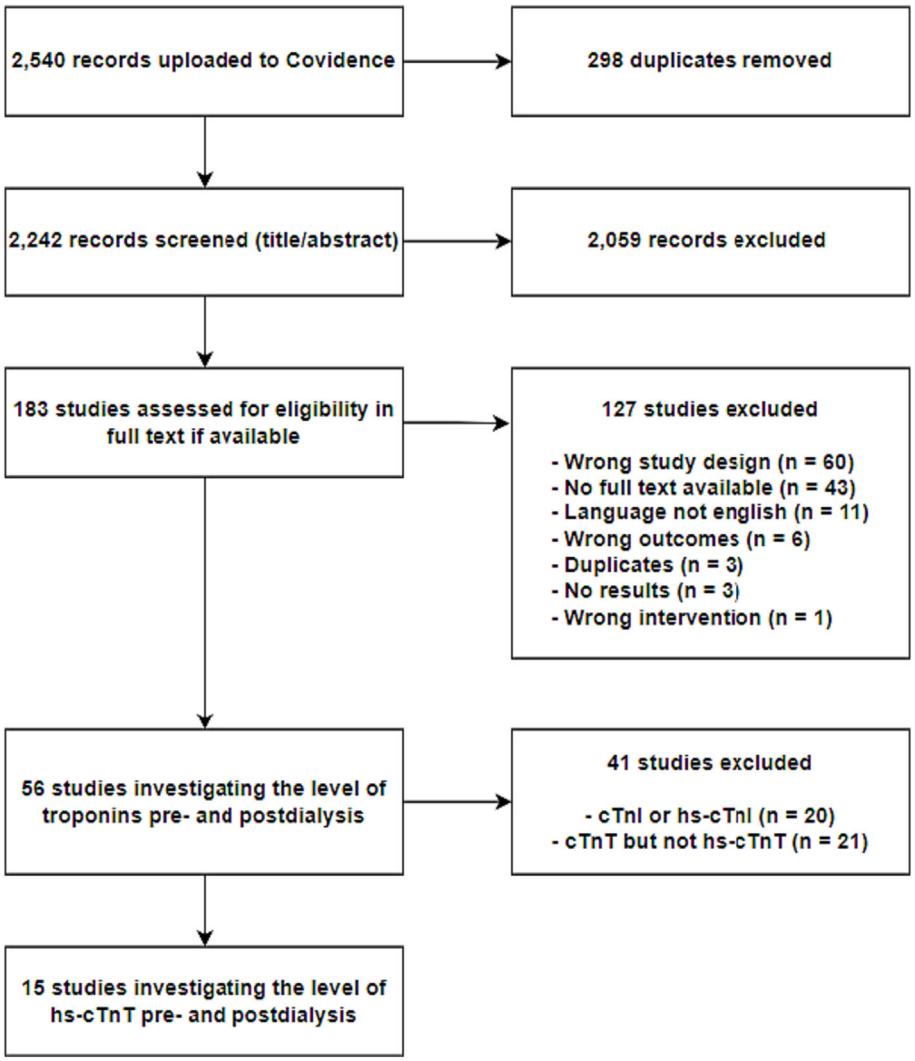

FIGURE 1 Flowchart showing the selection process.

to be based on adults (>18 years) without any symptoms or signs of acute heart ischemia. Only studies using a hs-cTnT assay were included and only full-text articles in English were accepted.

Several databases were searched: ClinicalTrials.gov, Cochrane Library, Embase, MEDLINE, and Web of Science. The first search took place in 2019 and was repeated in September 2022. The search string consisted of "renal dialysis" combined with "troponin" and for each of these several adjacent terms. The identified studies matching the search criteria were uploaded to Covidence,[12] which is a tool for systematic reviews. The search was assisted by two librarians. The full search string is available upon request to the corresponding author.

Each of the uploaded records was independently evaluated by two of the authors. First, records were included or excluded based on title and abstract, and the selected records from this step were evaluated in full text for eligibility. Disagreements throughout the selection process were discussed in order to reach consensus.

Initially, the focus were both on cTnT and cTnI regardless of assay type (high-sensitive or not), but it was later decided to focus solely on hs-cTnT in this review (see Figure 1).

One author extracted the relevant data for this review and another author checked the correctness of these data. Information on year of publication, country, study design, number of participants, age, gender, ischemic heart disease, diabetes, hypertension, dialysis type, coupled pre- and post hs-cTnT concentrations, and eventual correction for ultrafiltration (UF) was extracted. For some included studies, the authors were contacted in order to obtain or confirm information, for example, the pre- and postdialysis values of hs-cTnT were not always available despite being measured.[7,13,14]

The number of participants presented in Table 1 is the number relevant for this review. This number can differ from the total number of participants in the original study, for example, only a subgroup is relevant in Wolley et al.[21]

If the RRT was described as HD, this was assumed not to include other modalities as HDF or hemofiltration.

All pre- and postdialysis hs-cTnT values in the results section are in ng/L. Conversion of the original unit has taken place in several cases. The pre- and postdialysis values are mean or median values depending on the original article. Both values corrected and not corrected for hemoconcentration due to UF have been included in this systematic review. If the authors did not mention correction for hemoconcentration, values were assumed to be uncorrected.

From the mean/median pre- and postdialysis values, absolute and relative changes were calculated as follows:

$$\text{Absolute change} = \text{postdialysis value} - \text{predialysis value}$$

$$\text{Relative change}\,(\%) = \frac{\text{postdialysis value} - \text{predialysis value}}{\text{predialysis value}} \times 100$$

The QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool[23] was used to evaluate the quality of all included articles in this review. However, the domains "index test" and "reference standard" were not applicable for this review and were replaced by "dialysis" and "troponin". Hereby, the four domains were the following: patient selection, dialysis, troponin, and flow/timing. For all studies, two of the authors independently evaluated the quality within each domain. Risk of bias assessment took place for all domains and applicability assessment for all domains except flow/timing. Disagreements in the assessments were discussed in order to reach consensus.

This review was prepared with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 checklist as a template.[24] The protocol was registered on PROSPERO[25] on 10 July 2020 (ID: CRD42020157166).

3 | RESULTS

The literature search identified 2,540 records that were uploaded to Covidence. After removal of duplicates, 2,242 records were included in the title/abstract screening, where 2,059 records were excluded. The remaining 183 records were assessed in full text leading to the exclusion of 127 studies. The remaining 56 studies investigated the level of cardiac troponins pre- and postdialysis and 15 of these studies investigated the level of hs-cTnT pre- and postdialysis (see Figure 1).

Tables 1 and 2 present information about the included studies. The number of participants ranged from 10 to 275. The 15 articles contained 21 coupled pre- and postdialysis results of hs-cTnT, three for low-flux HD (LF-HD), six for high-flux HD (HF-HD), seven for HD not further specified, and five for HDF. The majority of authors (12/15) did not correct for UF. The predialysis mean and median values ranged from 52 to 111 ng/L and 42 to 82 ng/L, respectively. The postdialysis mean and median values ranged from 60 to 101 ng/L and 34 to 90 ng/L, respectively. Absolute changes varied from −42 to 15 ng/L and relative changes varied from −41 to 29%. LF-HD increased the hs-cTnT concentration with relative changes between 2 and 17%. HDF decreased the concentration with relative changes from −41% to −9%. Both increases and decreases were seen for HF-HD (−16% to 12%).

The QUADAS-2 bias and applicability assessment for the individual studies are shown in Figures 2 and 3. The risk of bias was highest within the domain "dialysis" with four studies placed in the "high" category and five in the "unclear" category. In accordance with this, the applicability concerns were also most pronounced within "dialysis" where two studies were placed in the "high" category and seven in the "unclear" category.

4 | DISCUSSION

In this systematic review, we found LF-HD to increase the hs-cTnT concentration and HDF to decrease the concentration. Results for HF-HD and unspecified HD are more heterogeneous.

Among the 15 included studies in this review, three studies[15,16,20] correct their results for the effect of hemoconcentration due to

TABLE 1 Study characteristics for the included studies.

Author	Year	Country	Study design	Population (n)	Age (years)	Gender	IHD or CAD	Diabetes	Hypertension
Badiou et al.[7]	2016	France	Longitudinal study	36	Median: 76	Women: 28% Men: 72%	NI	NI	NI
Cardinaels et al.[15]	2015	Holland	Prospective cohort study	13	Mean: 54	Women: 23% Men: 77%	Nine patients with cardiovascular disease, not specified	NI	77%
Chen et al.[2]	2017	Canada	Prospective cohort study	10	Mean: 77	Women: 30% Men: 70%	CAD: 70%	80%	100%
Emilian et al.[13]	2012	Luxembourg	Prospective cohort study	41	Median: 67	Women: 37% Men: 63%	Myocardial infarction: 12%	17%	49%
Flythe et al.[14]	2021	USA	Randomized crossover study	34[a]	Mean: 56	Women: 24% Men: 76%	CAD: 32%	50%	88%
Hassan et al.[6]	2014	Australia	Prospective cohort study	275	Median: 65	Women: 41% Men: 59%	Cardiac disease: 43%	53%	NI
Koycheva et al.[4]	2016	The Republic of North Macedonia	Prospective cohort study	48	Mean: 53	Women: 46% Men: 54%	NI	NI	NI
Laveborn et al.[16]	2015	Sweden	Randomized cross-over study	31	Mean: 62	Women: 45% Men: 55%	NI	55%	NI
Pianta et al.[17]	2012	Australia	Cross-sectional study	103	Median: 73	Women: 37% Men: 63%	CAD: 51%	47%	56%
Roberts et al.[18]	2018	Australia	Prospective cohort study	23	Mean: 68	Women: 26% Men: 74%	CAD: 35%	57%	NI
Skadberg et al.[5]	2016	Norway	Prospective cohort study	20[b]	Median: 64	Women: 20% Men: 80%	IHD: 40%	10%	80%
Ünlü et al.[19]	2020	Turkey	Prospective cohort study	70	NI[c]	Women: 39% Men: 61%	CAD: 0%	NI[c]	NI[c]
Wajdlich et al.[20]	2017	Poland	Prospective cohort study	50	Mean: 65	Women: 30% Men: 70%	IHD: 40%	36%	NI
Wolley et al.[21]	2013	New Zealand	Prospective cohort study	75	NI	NI	NI	NI	NI
Wongcharoen et al.[22]	2021	Thailand	Prospective cohort study	200	Mean: 62	Women: 45% Men: 56%	CAD: 13%	45%	91%

Abbreviations: CAD, coronary artery disease; IHD, ischemic heart disease; NI, no information.

[a]Thirty-four participants were included (baseline characteristics) but only 33 participants contributed to the results listed here.

[b]Twenty participants were included (baseline characteristics) but only 17 participants contributed to the results listed here.

[c]Baseline characteristics are available (n = 81), but there is a discrepancy with the number of participants written elsewhere (n = 70).

TABLE 2 Pre- to postdialysis changes of hs-cTnT. Authors are grouped according to RRT type.

Author	LF-HD/HF-HD/HDF	Correction for UF	Predialysis hs-cTnT (ng/L)	Postdialysis hs-cTnT (ng/L)	Absolute change (ng/L)	Relative change (%)
Laveborn et al.[16]	LF-HD	Yes	95 (mean)	101 (mean)	6	6
Wajdlich et al.[20]	LF-HD	Yes	82 (median)	84 (median)	2	2
Koycheva et al.[4]	LF-HD	No	60 (mean)	70 (mean)	10	17
Cardinaels et al.[15]	HF-HD (4 hours)	Yes	43 (median)	48 (median)	5	12
Cardinaels et al.[15]	HF-HD (8 hours)	Yes	42 (median)	36 (median)	−6	−14
Laveborn et al.[16]	HF-HD	Yes	84 (mean)	70 (mean)	−14	−16
Flythe et al.[14]	HF-HD	No	82 (median)[a]	90 (median)[a]	8	10
Roberts et al.[18]	HF-HD[b]	No	43 (median)	41 (median)	−2	−5
Skadberg et al.[5]	HF-HD	No	51 (median)	45 (median)	−6	−12
Chen et al.[2]	HD[c]	No	111 (mean)	100 (mean)[d]	−11	−10
Emilian et al.[13]	HD[c]	No	72 (median)[e]	59 (median)[e]	−13	−18
Hassan et al.[6]	HD[c]	No	60 (median)	58 (median)	−2	−3
Pianta et al.[17]	HD[c]	No	69 (median)	61 (median)	−8	−12
Ünlü et al.[19]	HD[c]	No	52 (mean)	67 (mean)	15	29
Wongcharoen et al.[22]	HD[c] (SII)	No	59 (median)	61 (median)	2	3
Wongcharoen et al.[22]	HD[c] (LII)	No	61 (median)	62 (median)	1	2
Cardinaels et al.[15]	HDF (4 hours)	Yes	46 (median)	42 (median)	−4	−9
Cardinaels et al.[15]	HDF (8 hours)	Yes	44 (median)	34 (median)	−10	−23
Laveborn et al.[16]	HDF	Yes	102 (mean)	60 (mean)	−42	−41
Badiou et al[7]	HDF	No	65 (median)[e]	40 (median)[e]	−25	−38
Wolley et al[21]	HDF[f]	No	76 (median)	66 (median)	−10	−13

Abbreviations: LII, long interdialysis interval; SII, short interdialysis interval; UF, ultrafiltration.
[a]The authors were contacted to obtain these values. The medians are for both groups combined, as it was not possible to obtain medians according to intervention.
[b]The majority (91%) uses high-flux dialyzers at baseline.
[c]No information about LF-HD/HF-HD.
[d]The postdialysis mean value is not mentioned but can be calculated from data in the article.
[e]Figures in the articles show the pre- and postdialysis values. We contacted the authors to obtain the precise values.
[f]Mainly HDF but no percentage given.

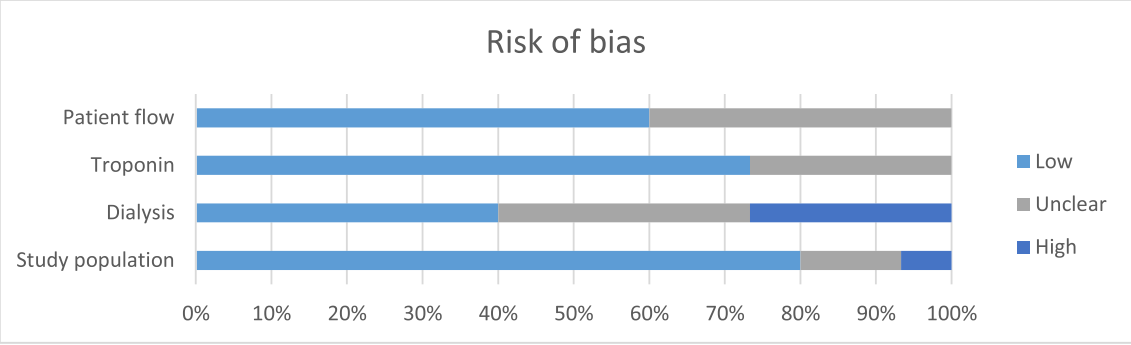

FIGURE 2 QUADAS-2 risk of bias assessment within four domains. The figure shows the proportion of included studies with a low, unclear and high risk of bias.

UF. To briefly explain this effect, excess fluid is drawn from patients during HD and HDF. As a result of this, the concentration of blood components increases when looking at this effect separately. For this reason, it can be expected that studies correcting for this see a greater decrease than otherwise. In the clinic, results are probably not corrected, making the uncorrected estimates easier to apply here.

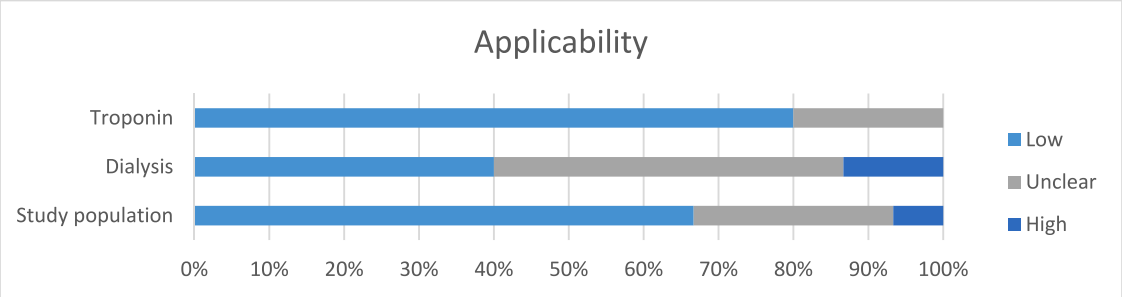

FIGURE 3 QUADAS-2 applicability assessment within three domains. The figure shows the proportion of included studies with a low, unclear and high concern regarding applicability.

Table 2 presents pre- to postdialysis hs-cTnT change estimates according to the type of RRT. When looking at both corrected and uncorrected estimates, three estimates are based on LF-HD[4,16,20] and all report an increase in hs-cTnT after HD. Six estimates (corrected and uncorrected) are available for HF-HD[5,14–16,18] and they range from −16% to 12%. However, one uncorrected estimate[14] are based on patients with a large UF (mean 2.7 L at baseline), increasing the effect from hemoconcentration due to UF. Omitting this estimate, four of the remaining five HF-HD estimates are negative (i.e., decreases), but there are no obvious explanation for the discrepancy between these four negative estimates and the one positive estimate (i.e., increase). Sixteen HD estimates (corrected and uncorrected) are presented in this systematic review, and for seven of these, there are no information regarding LF-HD or HF-HD.

In addition to these differences, it varies whether results are presented as medians or means. If the results are not normally distributed, medians are preferred.

Because of the mentioned differences with regard to LF-HD/HF-HD/HDF and correction/no correction, a meta-analysis was not meaningful. Estimates of the relative hs-cTnT change range from −41% to 29%, indicating the need for subanalysis to explain this result. Our findings highlight the challenges of using the recommended 20% change of troponin approach in patients undergoing HD/HDF.

The most pronounced increase (29%) is based on uncorrected results for patients with a large UF,[19] which contribute to the increase as explained above.

The calculation of both absolute and relative hs-cTnT change estimates in this review is based on mean or median pre- and postdialysis hs-cTnT values from the 15 included studies. However, the change of a mean or median value is not necessarily the best way to evaluate the change. Chen et al.[2] calculated the relative change for each participant and used these to calculate a mean relative difference. This value is not necessarily similar to the relative change of a mean or median value. To illustrate this, Chen et al. found an average relative change of −12% calculated from the individual relative changes, while our estimate in Table 2 on −10% is calculated from pre- and postdialysis mean values. However, as the mean or median pre- and postdialysis values were mentioned more frequently in the original articles, we used these to calculate change estimates in order to make the same estimates for each study, thus, making them easier to compare.

This systematic review is, to our knowledge, the first to investigate the effect of HD and HDF on hs-cTnT. It gives an overview of the existing knowledge and makes it easier to interpret serial hs-cTnT results in relation to HD/HDF.

A limitation to this review is the heterogeneity of the included studies and hereby the lack of a meta-analysis. It varies whether they focus on LF-HD, HF-HD, or HDF, and for several of the studies, it is not mentioned whether the HD is LF-HD or HF-HD. Additionally, the majority of studies do not correct for UF but some do. All this makes comparison complex.

Additionally, it must be remembered that the hs-cTnT changes shown here are strictly pre- to postdialysis changes. Chen et al. have shown that hs-cTnT returns to the predialysis concentration within the first day.[2]

The underlying mechanism for hs-cTnT change remains unclear. In the cases with decreasing concentration, it may seem obvious that hs-cTnT is filtered out to some degree during dialysis. However, an experimental HD model could not show cTnT in the dialysate fluid (measured with a non-hs-cTnT assay) and while cTnI adhered to the dialysis membrane, this was not the case for cTnT.[26]

Future research should pay attention to the differences seen between LF-HD, HF-HD, and HDF and investigate changes for these separately. If new types of RRT are implemented, for example, HD with medium cut-off membranes,[27] estimates of pre- to postdialysis hs-cTnT changes for these are needed.

5 | CONCLUSION

Our results show that LF-HD increases the blood concentration of hs-cTnT (2–17%), while HDF decreases the hs-cTnT concentration (−41% to −9%). Results for HF-HD and unspecified HD are more heterogeneous.

This systematic review can help with the assessment of patients with ESRD suspected of ACS in relation to HD/HDF treatment.

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CONFLICT OF INTEREST STATEMENT

None.

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